



DEPARTMENT OF THE ARMY
U.S. ARMY MEDICAL MATERIEL DEVELOPMENT ACTIVITY
622 NEIMAN STREET
FORT DETRICK, MARYLAND 21702-5009

October 25, 2004

REPLY TO
ATTENTION OF:

Office of the Commander

SUBJECT: BB-IND 157 - Tularemia Vaccine, Live, Attenuated (Serial No. 148) [Response to FDA Request for Information]

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Vaccines Research and Review
Division of Vaccines and Related Products Applications
1401 Rockville Pike
HFM-99, Suite 200 North
Rockville, Maryland 20852-1448

Dear Sir or Madam:

Enclosed in triplicate are copies of the Summary of Safety for Live, Attenuated *Francisella Tularensis* (Tularemia) Vaccine, NDBR 101 or RSI-GSD 213 Product.

This submission includes the following:

- Introduction
- Objectives
- Overview of Studies
- Exposure
- Demographic and Baseline Data
- Definitions
- Methods
- Adverse Events Reported During Clinical Trials
- Clinical Laboratory Data
- Additional Human Safety Information
- Special Pharmacologic Properties
- Summary and Conclusions
- References
- Appendix

The point of contact for regulatory questions concerning this submission is Ms. Kathie Mantine at 301-619-2809, facsimile 301-619-0197, or electronic mail kathie.mantine@amedd.army.mil.

Sincerely,

Jérôme F. Pierson
Colonel, Medical Service Corps
Commander

Enclosures

CF:
USAMMDA, MCMR-UMP
USAMRIID-PDRA

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: November 30, 2002
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSER

Office of The Surgeon General, Department of the Army

3. ADDRESS (Number, Street, City, State and Zip Code)

Commanding General, U.S. Army Medical Research and Materiel Command
ATTN: MCMR-RCQ-RA
504 Scott Street
Fort Detrick, MD 21702-5012

2. DATE OF SUBMISSION

25 OCT 04

4. TELEPHONE NUMBER (Include Area Code)

301-619-2165

5. NAME(S) OF DRUG (Include all available names: Trade, Generic, Chemical, Code)

Tularemia Vaccine, Live, Attenuated

6. IND NUMBER (If previously assigned)

BB-IND 157

7. INDICATION(S) (Covered by this submission)

Prevention of Tularemia

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:

☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER

(Specify)

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), DRUG MASTER FILES (21 CFR Part 314.420), AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.

SERIAL NUMBER

1 4 8

11. THIS SUBMISSION CONTAINS THE FOLLOWING: (Check all that apply)

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)

☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):

INFORMATION AMENDMENT(S):

IND SAFETY REPORT(S):

☐ NEW PROTOCOL

☐ CHEMISTRY/MICROBIOLOGY

☐ INITIAL WRITTEN REPORT

☐ CHANGE IN PROTOCOL

☐ PHARMACOLOGY/TOXICOLOGY

☐ FOLLOW-UP TO A WRITTEN REPORT

☐ NEW INVESTIGATOR

☐ CLINICAL

☐ RESPONSE TO FDA REQUEST FOR INFORMATION

☐ ANNUAL REPORT

☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED

☒ OTHER FDA Request for information

(Specify)

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION

☒ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

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CDR/DBIND/DGD RECEIPT STAMP

DDR RECEIPT STAMP

DIVISION ASSIGNMENT:

IND NUMBER ASSIGNED:

12. CONTENTS OF APPLICATION

This application contains the following items: (Check all that apply)

- ☐ 1. Form FDA 1571 [21 CFR 312.23(a)(1)]
- ☐ 2. Table of Contents [21 CFR 312.23(a)(2)]
- ☐ 3. Introductory statement [21 CFR 312.23(a)(3)]
- ☐ 4. General Investigational plan [21 CFR 312.23(a)(3)]
- ☐ 5. Investigator's brochure [21 CFR 312.23(a)(5)]
- ☐ 6. Protocol(s) [21 CFR 312.23(a)(6)]
- ☐ a. Study protocol(s) [21 CFR 312.23(a)(6)]
- ☐ b. Investigator data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
- ☐ c. Facilities data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
- ☐ d. Institutional Review Board data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data [21 CFR 312.23(a)(7)]
- ☐ Environmental assessment or claim for exclusion [21 CFR 312.23(a)(7)(iv)(e)]
- ☐ 8. Pharmacology and toxicology data [21 CFR 312.23(a)(8)]
- ☐ 9. Previous human experience [21 CFR 312.23(a)(9)]
- ☐ 10. Additional information [21 CFR 312.23(a)(10)]

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NOIF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

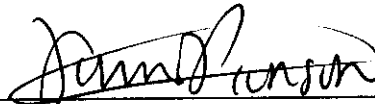
14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE
JEROME F. PIERSON, COL, MS
Commanding, U.S. Army Medical Materiel Development Activity

17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE



18. ADDRESS (Number, Street, City, State and Zip Code)

622 Neiman Street
Fort Detrick, MD 21702-5009

19. TELEPHONE NUMBER (Include Area Code)

301-619-7643

20. DATE

1 Nov 94

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please DO NOT RETURN this application to this address.

Summary of Safety for Live, Attenuated *Francisella tularensis* (Tularemia) Vaccine, NDBR 101 or TSI-GSD 213 Product

Contributing Protocols:

Open-label vaccination studies using NDBR 101 product:
99-2
87-9
68-4/68-4A
65-8
65-7
65-4
AB-104

Open-label vaccination studies using TSI-GSD 213 product:
91-9
87-4

Aerosol challenge studies:
67-1
65-13/65-13A

Skin test study:
75-2

Sponsor:

Department of Defense
Office of The Surgeon General
Department of the Army
U.S. Army Medical Research and Materiel Command
Attn: MRMC-RCQ-RA
504 Scott Street
Fort Detrick, MD 21702-5012

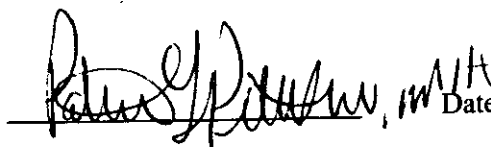
Date of the Report: October 22, 2004

The U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) is committed to providing this complete and audited summary of safety information as compiled from Final Integrated Clinical and Statistical Reports and the current Investigator's Brochure. Information contained in this publication is the property of the Department of the Army and USAMRIID and is for official use only.

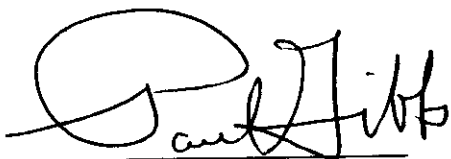
SIGNATURES

I have read this report and confirm that, to the best of my knowledge, it accurately describes the safety aspect of the tularemia vaccine.

Patricia L. Petitt, DO, MPH
Principal Investigator:

 Date: 22 Oct 04

Paul H. Gibbs, MS
Trial Biostatistician:

 Date: 22 OCT 04

Elaine R. Berry
Medical Writer:

Elaine R. Berry Date: 10/22/04

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Integrated Summary of Safety, Tularemia Vaccine

Date: September 17, 2004

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SYNOPSIS

Title:	Safety Summary for Live, Attenuated <i>Francisella tularensis</i> (Tularemia) Vaccine, NDBR 101 or TSI-GSD 213 Product
Objective:	This report contains a compilation of safety data from 12 final study reports submitted in support of BB-IND 157.
Trials and Design:	Open-label vaccination studies using NDBR 101 product: 99-2 87-9 68-4/68-4A 65-8 65-7 65-4 AB-104 Open-label vaccination studies using TSI-GSD 213 product: 91-9 87-4 Aerosol challenge studies: 67-1 65-13/65-13A Skin test study: 75-2
Number of Subjects:	1,270 subjects were enrolled as follows: 1,064 subjects enrolled in NDBR 101 product studies 163 subjects enrolled in TSI-GSD 213 product studies 32 subjects enrolled in aerosol challenge studies 11 subjects enrolled in skin test study

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Population:		NDBR 101 Product Studies	TSI-GSD 213 Product Studies	Aerosol Challenge Studies	Skin Test Study
Age (years)	<19	25	4	-	-
	20-29	463	91	32	2
	30-39	220	53	-	6
	40-49	228	15	-	1
	50-59	98	-	-	-
	60-69	21	-	-	-
	over 70	-	-	-	-
	no data	9	-	-	-
Race	White	932	106	29	10
	Black	67	47	3	-
	Hispanic	2	6	-	-
	Asian	11	3	-	-
	Other	4	-	-	-
	Unknown	48	1	-	1
Gender	Male	946	131	32	10
	Female	118	32	0	1

**Dose and Route of
Administration of
Reference Drugs:**

For NDBR 101 and TSI-GSD 213 product vaccination studies:

Single dose, approximately 0.1 mL of vaccine product placed on skin and pierced 15-30 times with a bifurcated needle (multiple puncture technique)

For aerosol challenge studies:

The number of low dose and high dose challenge organisms was specific to the study and ranged from 2,403 to 36,368 virulent *F. tularensis* organisms delivered via modified Henderson apparatus.

For skin test study:

Single dose (0.1 mL) of freshly reconstituted Foshay skin test antigen (1:1000 dilution of phenol-killed Foshay vaccine), injected intracutaneously (IC) into the forearm.

Also used:

Sodium chloride USP 0.9% (injection) or sterile tryptose saline (aerosol) as placebo when indicated in the study procedures.

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Adverse Events Recorded:	NDBR 101 Product Studies (N=1,064)	TSI-GSD 213 Product Studies (N=163)	Aerosol Challenge Studies (N=32)	Skin Test Study (N=11)	Total (N=1,270)
Body System					
Body as a Whole	85	68	82	0	235
Cardiovascular	0	0	0	0	0
Digestive	0	4	0	0	4
Eyes, Ears, Nose, Throat	7	6	31	0	44
Gastrointestinal	5	27	7	0	39
Hemic & Lymphatic	54	35	0	0	89
Metabolic & Nutritional	0	0	0	0	0
Musculoskeletal	17	28	25	0	70
Nervous System	4	6	3	0	13
Respiratory	1	20	6	0	27
Skin & Appendages	295	298	4	0	597
Urogenital	0	1	0	0	1
Total (percentage of total)	468 (42%)	493 (44%)	158 (14%)	0 (0%)	1,119 (100%)

N=number of subjects

Note: AEs were not recorded in a consistent manner across the studies or among the study personnel.

Elevated Liver Function Test Values Recorded:

	NDBR 101 Product Studies					
	Protocol 87-9 Lot 11		Protocol 68-4 Lot 4		Protocol 68-4A (aerosol challenge)	
	N	%	N	%	N	%
ALT (0 - 50 IU/L)	22	18.2	0	n/a	2	10
AST (10 - 42 IU/L)	16	13.2	0	n/a	2	10

TSI-GSD 213 Product Studies

	Protocol 91-9				Protocol 87-4			
	Lot 2R-85		Lot 3-85		Lot 1R-85		Placebo	
	N	%	N	%	N	%	N	%
ALT (0 - 50 IU/L)	5	10.6	2	4.3	9	26.5	6	17.1
AST ¹ (10 - 42 IU/L)	5	10.6	1	2.1	12	35.3	11	31.4

¹ AST reference range in Protocol 91-9 was 0 - 50 IU/L

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Summary and Conclusions:

There are two tularemia vaccine products: NDBR 101 and TSI-GSD 213, both of which are live and attenuated. The manufacturing process is summarized in this report.

This report reviews safety data from 12 clinical trials. In these trials, a total of 1,270 subjects were exposed to tularemia, either by vaccination, aerosol challenge, or skin test. Most subjects were male (88%), white (85%), and between the ages of 20 and 29 (46%). Vaccination was a single dose of approximately 0.1 mL vaccine product placed on the arm and pierced 15 to 30 times with a bifurcated needle (multiple puncture technique). Aerosol challenge exposed subjects to a range of up to 36,368 virulent *F. tularensis* organisms using a modified Henderson apparatus. The skin test was a single dose (0.1 mL) of freshly reconstituted Foshay skin test antigen (1:1000 dilution of phenol-killed Foshay vaccine), injected IC into the forearm.

The analysis in this report is based on recorded adverse events (AEs). An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational drug (vaccine) that does not necessarily have a causal relationship with this treatment. An AE, therefore, can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product (e.g., tularemia vaccine, aerosol, or skin test antigen) whether or not causally related.

The percentages of AEs reported among the NDBR 101 and TSI-GSD 213 products appear to be relatively equal (42% vs. 44%, respectively, across all studies); however, there were substantially more subjects in the NDBR 101 studies than the TSI-GSD 213 studies (1,064 vs. 163, respectively). There were 468 AEs reported among the 1,064 subjects vaccinated by an NDBR 101 product and 493 AEs reported among the 163 subjects vaccinated by a TSI-GSD 213 product. The smaller number of AEs reported in the NDBR 101 studies may be because the NDBR 101 product was less reactogenic than the TSI-GSD 213 product or because data collection methods were more thorough in the TSI-GSD 213 studies. The TSI-GSD 213 studies were conducted for the most part after the NDBR 101 studies when reporting guidances became more stringent (i.e., Good Clinical Practices).

There were 158 AEs reported among the 32 subjects in the aerosol challenge studies accounting for 14% of the total number of AEs reported across all studies. No AEs were reported by subjects in the skin test study.

The safety profile of the tularemia vaccine is mainly characterized by typical vaccination reactions. Of the 12 body systems, 53% of the AEs were in the Skin and Appendages body system with papule (13%), lesion and lesion at injection site (11%), and pruritus (7%) being the top 3 AEs reported. AEs in the Body as a Whole, Hemic and Lymphatic, and Musculoskeletal body systems accounted for 21%, 8%, and 6.3%, respectively, with the top AEs reported being headache (7.4%), fever (4.7%), malaise (4.7%), lymphadenopathy (8%), and myalgia (4.4%). The remaining 8 body systems accounted for less than 12% of the recorded AEs: Cardiovascular (no AEs reported), Digestive (0.4%), Eyes, Ears, Nose, Throat (4%), Gastrointestinal (3.5%), Metabolic and Nutritional (no AEs reported), Nervous (1.2%), Respiratory (2.4%), and Urogenital (0.1%).

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Summary and Conclusions (continued):

Two serious adverse events (SAEs), defined as resulting in death, a life-threatening AE, an inpatient hospitalization, a persistent or significant disability/incapacitation, or a congenital anomaly/birth defect, were documented, one in Protocol 87-4 and the other in Protocol 87-9. The subject in Protocol 87-4 was hospitalized with fever and diffuse adenopathy but was later diagnosed with Hodgkin's disease, nodular sclerosing variety, that was most likely present prior to the subject's enrollment in the study. It has, therefore, been determined that this SAE was unrelated to the administration of the vaccine. No safety reports were required to be submitted to FDA.

The subject in Protocol 87-9 was seen as an outpatient in the emergency room complaining of eye pain and loss of vision. The subject had been vaccinated 4 years prior to the AE, was enrolled in multiple protocols, and was also predisposed to HLA-B27-associated uveitis because of an autoimmune condition. The causal relationship of the SAE reported for the Protocol 87-9 subject was thoroughly reviewed and was conclusively determined unlikely to be related to the administration of the vaccine. No subjects developed an actual or modified form of the natural disease, and no systemic allergic reactions or Guillain-Barré syndrome (GBS) were attributed to the live, attenuated tularemia vaccine(s), aerosol, or skin test.

Liver function test (LFT) data were collected in only four of the studies. None of the 20 subjects vaccinated with Lot 4 (Part I of Protocol 68-4) had an LFT out of the established reference range and only 2 subjects (10%), both noncontrols in the high-dose challenge group, had an alanine aminotransferase (ALT) and aspartate aminotransferase (AST) value outside the established reference range. Data available on 121 subjects vaccinated with NDBR 101, Lot 11 (Protocol 87-9) showed 22 subjects (18.2%) had an elevated ALT value and 16 subjects (13.2%) had an elevated AST level. Most of the elevated readings were short-lived as elevated ALT values for 14 of the 22 subjects (64%) and elevated AST values for 13 of the 16 subjects (81%) returned to within normal limits at Day 1.

In the TSI-GSD 213 studies, data were not available on all 47 subjects in each treatment group (Protocol 91-9); however, elevated ALT levels were seen in 5 of 42 subjects (10.6%) vaccinated with Lot 2R-85 and in 2 of 45 subjects (4.3%) vaccinated with Lot 3-85. Elevated AST levels were reported in 5 of 42 subjects (10.6%) vaccinated with Lot 2R-85 and 1 of 46 subjects (1.6%) vaccinated with Lot 3-85. In Protocol 87-4, elevated ALT levels were seen in 9 of 34 subjects (26.5%) vaccinated with TSI-GSD 213, Lot 1R-85 and in 6 of 35 subjects (17.1%) given placebo. Elevated AST levels were also seen in 12 of 34 subjects (35.3%) vaccinated with Lot 1R-85 and in 11 of 35 subjects (31.4%) given placebo.

In summary, the tularemia vaccine was well tolerated in healthy adult volunteers as evidenced by the low number of reported AEs and by the number of expected vs. unexpected AEs. Likewise, aerosol exposure and skin test exposure did not cause an inordinate number of unexpected AEs.

ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/Term	Definition
AE(s)	adverse event(s)
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
A-RFC	active-rosette-forming lymphocyte
AST	aspartate aminotransferase
BID	twice a day
BV	blue variant
CI	confidence interval
cm	centimeter
CPK	creatine phosphokinase
ESR	erythrocyte sedimentation rate
FA	febrile agglutination
FDA	U.S. Food and Drug Administration
g	gram
g/dL	grams per deciliter
GBS	Guillain-Barré syndrome
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GM	geometric mean
GMT	geometric mean titer
GV	gray variant
HCT	hematocrit
HGB	hemoglobin
IC	intracutaneous
ID	intra dermal
IM	intramuscular
IND	Investigational New Drug
IU/L	units per liter, International System of Units
L	liter
LDH	lactic dehydrogenase
LFT(s)	liver function test(s)
LT	lymphocyte transformation
LVS	live vaccine strain
MA	microagglutination
MRVS	Medical Research Volunteer Subjects
μL	microliter
mL	milliliter
mm	millimeter
mm/hr	millimeters per hour
N	number of subjects
NDBR	National Drug Biologic Research Company
p	probability

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Abbreviation/Term	Definition
PC	percutaneous (scarification)
PE	postexposure event after challenge (e.g., an AE following challenge)
PI	Principal Investigator
SAE(s)	serious adverse event(s)
SC	subcutaneous
SCHU-S4	virulent strain of <i>F. tularensis</i> used in challenge
SD	standard deviation
SIP	Special Immunizations Program
T _{max}	maximum temperature
TSI	The Salk Institute
TSI-GSD	The Salk Institute-Government Services Division
USAMRIID	U.S. Army Medical Research Institute of Infectious Diseases
USAMU	U.S. Army Medical Unit (now known as USAMRIID)
USP	U.S. Pharmacopeia
VAERS	Vaccine Adverse Event Reporting System
WBC	white blood cell
°C	degrees Celsius
°F	degrees Fahrenheit

1 Introduction

Francisella tularensis, formerly known as *Pasteurella tularensis*, the causative bacterium of tularemia, was isolated in 1912, but it was not until 1919 that Edward Francis made the association with the human disease “deer fly fever” [1]. This Gram-negative bacterium is responsible for endemic and epidemic diseases in animals and humans [2]. The organism can infect many different vertebrate and invertebrate hosts, but selects mostly rodents and lagomorphs. Transmission to humans is generally via an insect vector such as ticks, mosquitoes, or biting flies, or from the handling of contaminated animal products or carcasses. It may also be acquired by consuming contaminated meat or from aerosol exposure. The terms *F. tularensis* and *P. tularensis* may be used interchangeably in this report.

Clinical tularemia varies in severity depending on the virulence of the organism, the route of entry, the extent of system involvement, and the immune status of the host. Following an incubation period of 3 to 5 days, individuals have an abrupt onset of fever, chills, headache, malaise, anorexia, and fatigue [3]. Individuals may present with single or overlapping presentations of the disease, including ulceroglandular, glandular, oculoglandular, pharyngeal, typhoidal, or pneumonic [2-6].

Ulceroglandular tularemia is the most common presentation and is generally acquired through insect bites or contact with animals infected with the organism. Individuals present with enlarged and localized tender lymph nodes. This form of the disease generally lasts 2 to 3 weeks, with some individuals suffering chronic fatigue for several months. Glandular tularemia presentation is similar to that of ulceroglandular tularemia, but without skin lesions. These two forms account for 75% to 85% of all cases of tularemia [7].

Oculoglandular tularemia occurs when the organism enters the conjunctiva either from rubbing the eyes with contaminated fingers or from exposure to liquids or aerosols. Presentation initially is with photophobia, increased lacrimation, painful conjunctivitis, and edema of the eyelid. Small yellowish conjunctival ulcers or papules may be present. Localized tender lymphadenopathy may occur in the preauricular, submandibular, or cervical lymph nodes.

Oropharyngeal and gastrointestinal (GI) tularemia occurs when the organisms enter the body through the oropharynx. This may occur from ingesting contaminated food or water. Symptoms include severe throat pain due to acute exudative or membranous pharyngitis. Exudative tonsillitis may also be present. Lymphadenopathy of the cervical, parotid, and retropharyngeal nodes may occur, and there may be abscess formation. Symptoms may also include diarrhea, abdominal pain, nausea, vomiting, and GI bleeding [8].

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Typhoidal tularemia, which is the more serious form of the disease, occurs commonly in laboratory workers exposed by aerosol or oral routes. This form is characterized by fever, malaise, headache, myalgias, pneumonic infiltrates on x-ray, severe prostration, anorexia, nausea, vomiting, sore throat, cough, and diarrhea in any combination, but without associated prominent localized lymphadenopathy. Physical examination may reveal mild pharyngitis and mild cervical adenopathy, meningismus, and diffuse abdominal pain. Hepatosplenomegaly is generally not seen in the initial presentation but may occur with prolonged duration of the disease. Diarrhea is common but is typically watery and without blood. Secondary pulmonary and pleural involvement is common, particularly in laboratory-acquired cases. The disease lasts 3 to 6 weeks, frequently with chronic fatigue that lasts for several months. A poor prognosis is indicated for individuals suffering from pneumonia or pleuritis; death is more common in the typhoidal form of the disease.

Pneumonic tularemia is characterized by pulmonary symptoms such as fever, cough with minimal or no sputum production, substernal tightness, and pleuritic chest pain. Symptoms are similar to those seen in atypical pneumonia. Hemoptysis is uncommon. Chest x-ray may show subsegmental or lobar infiltrates, hilar adenopathy, pleural effusion, and apical and/or miliary infiltrates. Pneumonic tularemia may occur from direct inhalation of the organism or from secondary hematogenous spread to the lung. Sheep shearers, farmers, and laboratory workers are at particular risk for pneumonic tularemia.

Two biovars of *F. tularensis* have been recognized. Type A is the dominant biovar in North America and highly virulent. Without treatment the mortality rate from infection of a Type A biovar is estimated between 5% to 7% [10]. Type B occurs predominantly in Asia and Europe, but also in North America and is considered to be less virulent than Type A.

Two live, attenuated vaccine products, NDBR 101 and TSI-GSD 213, were developed from the live vaccine strain (LVS) (Type B biovar) to help protect laboratory workers and others who might be at risk of exposure to tularemia. Lots from these two products were used in the protocols to support Investigational New Drug application (IND) BB 157. The specific lots and the particular protocols are listed in Table 1. Complete summaries of the NDBR 101 and TSI-GSD 213 products follow the table.

Table 1. Vaccine Lots Used in Investigational Protocols in Support of BB-IND 157

NDBR 101		TSI-GSD 213	
Investigational Protocol	Lot	Investigational Protocol	Lot
99-2	11	91-9	2R-85 and 3-85
87-9	11	87-4	1R-85
68-4/68-4A	4		
65-8	2 and 4		
65-7	4		
65-4	3		
AB-104	4 ¹		

¹ Other lots were used in the study, but only data from subjects vaccinated with Lot 4 were used in the Integrated Final Clinical and Statistical Report.

1.1 NDBR 101 Product

The *F. tularensis* Vaccine, Live, NDBR 101 is a lyophilized vaccine containing live *F. tularensis* bacteria and was administered to humans in a single dose by scarification (multiple puncture technique). The U.S. Army Medical Unit (USAMU, now known as U.S. Army Medical Research Institute of Infectious Diseases [USAMRIID]) began development of a live tularemia vaccine in 1956 from an ampoule of dehydrated live vaccine prepared by the Gamaleia Institute of Epidemiology and Microbiology, USSR. A vial of the Russian vaccine was reconstituted (within the expiration date of the product) with sterile distilled water. The reconstituted vaccine was streaked on peptone cysteine agar and incubated. The cultures were viewed under a dissecting microscope with oblique lighting. Two colony-type variants, one gray (GV) and the other blue (BV), were discernible. The BV proved to be more virulent and immunogenic than the GV in the mouse and the guinea pig. Subsequent studies demonstrated that lyophilization reduced virulence of the BV with no appreciable change in immunogenicity. The reconstituted BV was then passed through the mouse. After the fifth serial passage, blood of the moribund animal was cultured for *F. tularensis*, and the isolate was designated LVS. USAMU produced four lots (L1 through L4) of vaccine from the LVS [9].

The U.S. Army transferred the technology to manufacture the vaccine to the National Drug Biologic Research Company (NDBR), Swiftwater, Pennsylvania (later known as The Salk Institute [TSI]). In 1962, NDBR used Lots L3 and L4 to produce NDBR 101 Lots 1 to 11 under contract to the U.S. Army Medical Research and Development Command. LVS Lot L3 was used as the seed to produce *F. tularensis* Vaccine, Live, NDBR 101, Lots 1, 2, 3, 4, 5, and 6, and in 1964, Lot L4 was used to produce NDBR 101 Lots 9 and 11.

From 1970 to 1987, the NDBR 101 vaccine was distributed by the National Communicable Disease Center (now known as the Centers for Disease Control and Prevention), Atlanta, Georgia, under IND 309, and by the USAMU (USAMRIID) under BB-IND 157.

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Only NDBR 101 Lots 2, 3, 4, and 11 have been used in the protocols to support BB-IND 157. The lots of lyophilized product were kept in storage at a temperature between -30°C and -10°C. When reconstituted with 2 mL Sterile Water for Injection, USP, the Lot 2 vial contained approximately 1×10^9 viable organisms per mL, the Lot 3 vial contained approximately 2×10^9 viable organisms per mL, the Lot 4 vial contained approximately 3×10^9 viable organisms per mL, and the Lot 11 vial contained approximately 2.4×10^9 viable organisms per mL (Table 2).

Table 2. Composition of NDBR 101 Vaccine Lots Used in Clinical Studies under BB-IND 157¹

	Lot 2	Lot 3	Lot 4	Lot 11
Active Ingredients	LVS, attenuated, <i>F. tularensis</i>	LVS, attenuated, <i>F. tularensis</i>	LVS, attenuated, <i>F. tularensis</i>	LVS, attenuated, <i>F. tularensis</i>
Adjuvant	none	none	none	none
Preservative	none	none	none	none
Other Ingredients	none	none	Modified casein partial hydrolysate medium, sucrose gelatin agar stabilizer solution, glucose cysteine hemin agar	none
Reconstituted with	2 mL Sterile Water for Injection, USP	2 mL Sterile Water for Injection, USP	2 mL Sterile Water for Injection, USP	2 mL Sterile Water for Injection, USP
Viable organisms/mL after reconstitution	approximately 1×10^9	approximately 2×10^9	approximately 3×10^9	approximately 2.4×10^9

¹ Each lot consisted of >99% BV and <1% GV.

NDBR 101 was packaged in 5 mL vials containing enough lyophilized product to make 20 doses of vaccine when reconstituted. After reconstitution, vials were to be stored at 4°C and used within 8 hours.

1.2 TSI-GSD 213 Product

In 1985, TSI Government Services Division (GSD; TSI-GSD) located in Swiftwater, Pennsylvania, produced a live, attenuated vaccine strain of *F. tularensis* from NDBR 101, Lot 9, using a new production method in which cultures were grown in a peptone-cysteine agar with a gelatin stabilizer. Updated production procedures involved the use of fermenter cultures that were aerated by air sparging. For this reason, an antifoaming compound (Dow Corning® Medical Antifoam AF Emulsion, a nontoxic, water-dilutable, nonionic emulsion of silicone) was added. Concentration of the antifoam in the final product was approximately 14.3 parts per million (0.0007%). The lyophilized vaccine preparation contained no preservative. Control certificates are not available. The new lots of the vaccine, designated as TSI-GSD 213, did not differ substantively in

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composition from NDBR production lots. Two studies (Protocols 91-9 and 87-4) used lots from this new production method (Table 3).

Table 3. Composition of TSI-GSD 213 Vaccine Lots Used in Clinical Studies under BB-IND 157

	Lot 2R-85	Lot 3-85	Lot 1R-85
Active Ingredients	LVS, attenuated, <i>F. tularensis</i>	LVS, attenuated, <i>F. tularensis</i>	LVS, attenuated, <i>F. tularensis</i>
Adjuvant	none	none	none
Preservative	none	none	none
Other Ingredients	Dow Corning® Antifoam AF Emulsion (nontoxic, water- dilutable, nonionic emulsion of silicone)	Dow Corning® Antifoam AF Emulsion (nontoxic, water- dilutable, nonionic emulsion of silicone)	Dow Corning® Antifoam AF Emulsion (nontoxic, water- dilutable, nonionic emulsion of silicone)
Reconstituted with	20 mL Sterile Water for Injection, USP	2 mL Sterile Water for Injection, USP	20 mL Sterile Water for Injection, USP
Viable organisms/mL after reconstitution	approximately 3.1×10^8	approximately 1.9×10^9	approximately 7×10^8

Before reconstitution, vials were to be stored at -20°C. The lyophilized vaccine was reconstituted with 20 mL (Lot 2R-85 and 1R-85) or 2 mL (Lot 3-85) of Sterile Water for Injection, USP. When reconstituted, the 2R-85 vial contained approximately 3.1×10^8 viable organisms per mL; the 3-85 vial contained approximately 1.9×10^9 viable organisms per mL; and the 1R-85 vial contained approximately 7×10^8 viable organisms per mL. After reconstitution, vials were to be stored at 4°C and used within 8 hours.

1.3 Placebo

When the protocol indicated, Sodium Chloride Injection USP 0.9% was used as the placebo injection and sterile tryptose saline was used as the placebo aerosol.

2 Objectives

This report presents safety data (recorded adverse events [AEs] and out-of-reference range laboratory results) 12 investigational protocols conducted in support of BB-IND 157, including one study that was initiated prior to the activation of the IND (Protocol AB-104). Special consideration is given to transaminase levels that were a concern to the Food and Drug Administration (FDA) and led to the tularemia vaccine being placed on clinical hold on February 29, 2000.

3 Overview of Studies

In seven clinical studies (99-2, 91-9, 87-9, 65-8, 65-7, 65-4, AB-104) subjects were vaccinated with the NDBR 101 product; in 2 clinical studies (91-9 and 87-4) subjects were vaccinated with the TSI-GSD product or a placebo; 2 clinical studies (67-1 and 65-13/ 65-13A) were aerosol challenge studies; and 1 clinical study (75-2) was a skin test study.

For additional information or to review the raw SAS data, the reviewer is directed to the submission of that protocol's Final Integrated Clinical and Statistical Report. A table of the studies along with their serial numbers and submission dates are presented in Table 4.

Table 4. Serial Numbers of Submitted Final Integrated Clinical and Statistical Reports Filed in Support of BB-IND 157

Study Number	Serial Number	Date Submitted to FDA
NDBR 101 Products		
99-2	147	September 24, 2004
87-9	124	January 13, 2003
68-4/68-4A	128	April 14, 2003
68-4/68-4A Amendment	139	January 12, 2004
65-8	130	May 6, 2003
65-7	129	April 16, 2003
65-4	141	February 24, 2004
AB-104	142	April 8, 2004
TSI-GSD Products		
91-9	118	August 13, 2002
87-4	127	February 12, 2003
Aerosol Challenge Studies		
67-1	134	August 29, 2003
65-13/65-13A	136	October 17, 2003
Skin Test Study		
75-2	131	June 10, 2003

A synopsis of each of the studies is presented in Table 5. A description of each of the studies follows the table.

Table 5. Table of Tularemia Vaccine Studies

Protocol Number	Title	Study Description	Product/Lot	Study Dates
99-2	A Longitudinal Phase 2 Multi-Site Study for the Continued Evaluation of the Safety and Immunogenicity of a Live <i>Francisella tularensis</i> Vaccine, NDBR 101	Phase 2 study Conducted at USAMRIID 1 healthy adult subject	NDBR 101 Lot 11	April 6, 1999 to February 28, 2000 when IND placed on clinical hold
87-9	Evaluation of New Lots of Tularemia Vaccine, Protocol B: Comparative Assessment of <i>Francisella tularensis</i> Vaccine, Live, TSI-GSD 213 Lot 1R, and <i>Francisella tularensis</i> Vaccine, Live, NDBR 101 Lot 11 (Log A-4707)	Phase 2 study Conducted at USAMRIID & 18 extramural sites 284 healthy adult subjects Note: TSI-GSD 213 Lot 1R-85 not tested due to potential safety concerns	NDBR 101 Lot 11	September 1987 to December 1999
68-4/ 68-4A	Evaluation of Storage Stability of Tularemia Vaccine, Live, Attenuated NDBR 101, Lot 4	Phase 1, 2-part study; unblinded vaccination and aerosol challenge with inpatient component Conducted at USAMU 20 healthy adult male subjects (Project Whitecoat volunteers)	NDBR 101 Lot 4	August 28, 1967 to December 7, 1967
65-8	Evaluation of Attenuated Tularemia Vaccine (LVS) from National Drug [Biologic Research] Company	Phase 1 study comparing 2 lots of NDBR 101 Conducted at USAMU 20 active duty personnel, healthy adult male subjects	NDBR 101 Lots 2 and 4	October 13, 1964 to January 5, 1965
65-7	Evaluation of Attenuated Tularemia Vaccine (LVS) from National Drug [Biologic Research] Company	Phase NS ¹ unblinded outpatient study Conducted at USAMU 12 active duty personnel, healthy adult male subjects	NDBR 101 Lot 4	September 30, 1964 to October 30, 1964
65-4	Evaluation of Attenuated Tularemia Vaccine (LVS) from National Drug [Biologic Research] Company	Phase 1 unblinded, outpatient study Conducted at USAMU 7 active duty personnel, healthy adult subjects	NDBR 101 Lot 3	July 24, 1964 to August 22, 1964
AB-104	Evaluation of Stability and Protective Efficacy of Tularemia Vaccine Live, Attenuated, among At-Risk Personnel	Phase NS ¹ Conducted at USAMU & 4 extramural sites 722 healthy adult subjects enrolled; 720 completed	NDBR 101 Lot 4 ²	August 12, 1965 to October 19, 1988

¹ NS = Not stated in the study protocol.² Other lots were used in this study, but only data from subjects vaccinated with Lot 4 were reported in the Final Integrated Clinical and Statistical Report.**For Official Use Only**

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Table 5. Table of Tularemia Vaccine Studies (continued)

Protocol Number	Title	Study Description	Product/Lot	Study Dates
91-9	Evaluation of the Safety and Immunogenicity of a Live Bacterial Tularemia Vaccine in Normal Adult Volunteers	Phase 2 randomized trial comparing 2 lots of TSI-GSD product Conducted at Johns Hopkins University Center for Immunization and Research 94 healthy adult subjects	TSI-GSD Lot 2R-85 TSI-GSD Lot 3-85	November 1991 to March 1993
87-4	Evaluation of New Lots of a Tularemia Vaccine Protocol A: Initial Assessment of the Safety of <i>Francisella tularensis</i> Vaccine, Live, TSI-GSD 213, Lot IR-85	Phase 1 double-blind placebo study Conducted at USAMRIID 69 healthy adult subjects	TSI-GSD Lot IR-85	October 16, 1987 to April 19, 1991
67-1	Respiratory <i>Pasteurella (Francisella) tularensis</i> in Man	Phase NS ¹ human performance study prior to virulent or placebo challenge; no vaccination Conducted at USAMU 10 healthy adult male subjects (Project Whitecoat volunteers)	Aerosol challenge study with 18480 to 30156 virulent organisms or sterile tryptose saline placebo	August 8, 1966 to August 31, 1966
65-13/ 65-13A	Evaluation of Storage Stability of Living Vaccine Strain (LVS) of <i>Pasteurella tularensis</i> (65-13) Evaluation of Metabolic Changes in Immunized Subjects Exposed to Infectious Doses of <i>P. tularensis</i> (65-13A)	Phase NS ¹ virulent vs. placebo aerosol challenge plus metabolic balance studies; inpatient component Conducted at USAMU 22 active duty personnel, healthy adult male subjects Note: Vaccination in a previous study 65-8	Aerosol challenge study with 2500 to 25000 virulent organisms	January 6, 1965 to February 9, 1965
75-2	Evaluation in Volunteers of the Active-Rosette-Forming Lymphocyte (A-RFC) Test as an Assay for Previous Immunization to Tularemia	Phase NS ¹ unblinded outpatient skin test antigen study with challenge component; no vaccination Conducted at USAMRIID 11 healthy adult subjects	0.1 mL of skin test antigen (1:1000 dilution of phenol-killed Foshay tularemia vaccine)	March 5, 1975 to October 29, 1975

NS = Not stated in the study protocol.

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3.1 NDBR 101 Studies

3.1.1 Protocol 99-2, Log A-8573: A Longitudinal Phase 2 Multi-Site Study for the Continued Evaluation of the Safety and Immunogenicity of a Live *Francisella tularensis* Vaccine, NDBR 101

Protocol 99-2 was a Phase 2 study conducted at USAMRIID with one subject who was enrolled and vaccinated on February 1, 2000. On February 28, 2000, the FDA placed BB-IND 157 on clinical hold; however, the study remained open for 175 days postvaccination to allow for subject follow up. Initially, the study was to compare several lots of TSI-GSD 213 products with NDBR 101, Lot 11; however, due to perceived safety concerns all TSI-GSD 213 products were eliminated from the study.

3.1.2 Protocol 87-9, Log A-4707: Evaluation of New Lots of Tularemia Vaccine, Protocol B: Comparative Assessment of *Francisella tularensis* Vaccine, Live, TSI-GSD 213 Lot 1R, and *Francisella tularensis* Vaccine, Live, NDBR 101 Lot 11

Protocol 87-9 was a Phase 2 study conducted at USAMRIID and 18 extramural sites between September 1987 and December 1999. Due to perceived safety concerns with TSI-GSD 213 Lot 1R-85 in which preliminary results showed an unexpected number of subjects had elevated liver enzymes, the original protocol was amended to evaluate titer response and collect AE data from approximately 250 male and female subjects vaccinated with NDBR 101 Lot 11 only. There were no comparative or control groups.

3.1.3 Protocol 68-4 and 68-4A: Evaluation of Storage Stability of Tularemia Vaccine, Live, Attenuated NDBR 101, Lot 4

Protocol 68-4 was an inpatient, unblinded, two-part study designed to determine the 5-year storage stability of tularemia vaccine, live, attenuated, NDBR 101, Lot 4 by vaccinating subjects (Part I) and exposing them to low- (approximately 2,500 viable [SCHU-S4 strain of *F. tularensis*] organisms) or high-dose (approximately 25,000 viable [SCHU-S4 strain of *F. tularensis*] organisms) aerosol challenge (Part II). Twenty (20) active duty personnel at USAMU participated as volunteer subjects for this study conducted between August 28, 1967, and December 7, 1967. Vaccination (Part I) occurred on August 28, 1967; aerosol challenge (Part II) occurred on October 25, 1967.

Each study group in Part II (Group 1 - low-dose challenge, Group 2 - high-dose challenge) included 8 vaccinated subjects and 2 unvaccinated control subjects.

3.1.4 Protocol 65-8: Evaluation of Attenuated Tularemia Vaccine (LVS) from National Drug [Biologic Research] Company

Protocol 65-8 was a Phase 1 study conducted at USAMU between October 13, 1964, and January 5, 1965. The 2-year storage stability of NDBR 101, Lot 2 and Lot 4, tularemia vaccine, live, attenuated was to be determined. Additionally, the level of protection afforded vaccinated and unvaccinated volunteers after aerosol challenge with *F. tularensis* was to be evaluated under Protocol 65-13, as discussed in Section 3.3.2 of this report.

A total of 20 healthy adult male active-duty personnel at USAMU enrolled as volunteers and completed this study. No withdrawals were noted.

3.1.5 Protocol 65-7: Evaluation of Attenuated Tularemia Vaccine (LVS) from National Drug [Biologic Research] Company

Protocol 65-7 was an unblinded, outpatient study conducted at USAMU between September 30, 1964, and October 30, 1964. A total of 12 healthy adult male volunteers were enrolled in this protocol, all personnel at USAMU who required vaccination for protection against tularemia. Subjects were vaccinated with tularemia vaccine, live, attenuated, NDBR 101, Lot 4.

3.1.6 Protocol 65-4: Evaluation of Attenuated Tularemia Vaccine (LVS) from National Drug [Biologic Research] Company

Protocol 65-4 was an unblinded, outpatient study conducted at USAMU between July 24, 1964, and August 22, 1964, designed to evaluate local reactions and humoral microagglutination (MA) titers of personnel vaccinated with tularemia vaccine, live, attenuated, NDBR 101, Lot 3. A total of 7 healthy adult volunteers were enrolled in this protocol, all personnel at USAMU who required vaccination for protection against tularemia.

3.1.7 Protocol AB-104: Evaluation of Stability and Protective Efficacy of Tularemia Vaccine, Live, Attenuated, among At-Risk Personnel

Protocol AB-104 was an unblinded, outpatient study conducted at USAMU and four other extramural sites between August 12, 1965, and October 19, 1988, when the protocol became inactive. The study was designed to provide the means for active immunization of at-risk personnel and to investigate further the stability and protective efficacy of tularemia vaccine, live, attenuated, NDBR 101, Lot 4. Several different lots of NDBR 101 tularemia vaccine were used in this study; however, only data from Lot 4 were extracted for this report as it is the lot being used in the current vaccination program. A total of 722 healthy adult volunteers were enrolled in this protocol, 720 of whom received a primary vaccination and 2 who received a booster.

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3.2 TSI-GSD 213 Studies

3.2.1 Protocol 91-9, Log A-5588: Evaluation of the Safety and Immunogenicity of a Live Bacterial Tularemia Vaccine in Normal Adult Subjects

Protocol 91-9 was a Phase 2 study conducted at Johns Hopkins University Center for Immunization Research between November 1991 and March 1993. Safety and immunogenicity of two live bacterial tularemia vaccine lots (TSI-GSD 213, Lot 2R-85 and Lot 3-85) in approximately 100 healthy adult (male and female) subjects were evaluated. Forty-seven subjects received Lot 2R-85 and 47 subjects received Lot 3-85.

3.2.2 Protocol 87-4, Log A-4706: Evaluation of New Lots of a Tularemia Vaccine, Protocol A: Initial Assessment of the Safety of *Francisella tularensis* Vaccine, Live, TSI-GSD 213, Lot 1R-85

Protocol 87-4 (Log A-4706) was a Phase 1 study conducted at USAMRIID between October 16, 1987, and April 19, 1991. One hundred subjects were screened, 69 of whom were randomized between vaccine (N = 34) and placebo (N = 35) treatment groups in a double-blind fashion. The study was designed to determine the rate of AEs in subjects given vaccine and compare the rates against those for subjects given placebo and to test the hypothesis that the rate of SAEs for vaccinated subjects should be no greater than 5% (with 80% confidence interval [CI]) in a study of this size. The study was also designed to assess the immunogenic response to Lot 1R-85.

3.3 Aerosol Challenge Studies

3.3.1 Protocol 67-1: Respiratory *Pasteurella (Francisella) tularensis* in Man

Protocol 67-1 was conducted at USAMU from August 8, 1966, to August 31, 1966, with the intent to extend data on the impact of respiratory tularemia upon measured task performance. Additionally, the study was designed to evaluate alterations in erythrocyte metabolism through the study of enzyme systems during infection; to extend observations on alteration in glucose metabolism during infection; to redefine subtle changes in the diurnal patterns of whole blood amino acid; and to examine alterations in trace metals in blood and urine during infection.

Ten healthy male subjects (none of whom had documented previous exposure to tularemia) were admitted to an isolation ward and randomized into 2 groups (8 virulent-challenge, 2 placebo-challenge). Eight of the 10 subjects were challenged with a range of 18,480 to 30,156 virulent *F. tularensis* aerosol organisms (geometric mean [GM] of 23,679) and 2 were challenged with a placebo aerosol (sterile tryptose saline).

3.3.2 Protocol 65-13: Evaluation of Storage Stability of Living Vaccine Strain (LVS) of *Pasteurella tularensis* and Protocol 65-13A: Evaluation of Metabolic Changes in Immunized Subjects Exposed to Infectious Doses of *P. tularensis*

Protocol 65-13 was a follow-up study to Protocol 65-8 (Evaluation of Attenuated Tularemia Vaccine [LVS] from NDBR Company. See Section 3.1.3 of this document); and Protocol 65-13A was an arm of Protocol 65-13. The study was conducted from January 6, 1965, to February 9, 1965, and was designed to evaluate the level of protection afforded vaccinated and unvaccinated volunteers after aerosol challenge with *F. tularensis*. Protocol 65-13A was an inpatient study designed to obtain comparative data of nitrogen, mineral, and electrolyte balance in vaccinated subjects exposed to varying doses of *F. tularensis*.

All subjects (except unvaccinated controls) were vaccinated via scarification (multiple puncture technique) in Protocol 65-8 with tularemia vaccine NDBR 101 Lot 2 or Lot 4 and exposed to either a low-dose (approximately 2,500 organisms) or high-dose (approximately 25,000 organisms) aerosol challenge of virulent *F. tularensis*.

Participants were randomized into 4 groups (Group A, B, C, and D). Subjects in Groups A, B, and C participated in Protocol 65-13, whereas subjects in Group D participated in Protocol 65-13A. All 22 participants were active duty male personnel at USAMU. All vaccinated study subjects were hospital corpsmen. Control subjects (N = 6), however, listed painter, hospital assistant, typist, corpsman, student, and mill worker as a primary vocation.

3.4 Skin Test Antigen Study

3.4.1 Protocol 75-2: Evaluation in Volunteers of the A-RFC Test as an Assay for Previous Immunization to Tularemia

Protocol 75-2 was an unblinded outpatient study conducted at USAMRIID between March 5, 1975, and October 29, 1975. The purpose of the study was to determine if the A-RFC was a sensitive in vitro assay for detecting prior sensitization to *F. tularensis* in humans. The study was also designed to compare the efficacy of the opsonic and microagglutination antibody assays, the skin test, and the lymphocyte transformation (LT) assay in diagnosing previous exposure to *F. tularensis*; and to determine whether the lot of phenol-killed lyophilized tularemia skin test antigen (Foshay) had retained its diagnostic efficacy and low reactogenicity after 18 years in storage.

Eleven healthy adult volunteers were given 0.1 mL freshly reconstituted Foshay skin test antigen (1:1000 dilution of the phenol-killed Foshay tularemia vaccine) injected intracutaneously (IC) into the forearm (similar to tuberculin tine testing) using standard sterile techniques. Six of the subjects had prior exposure to the tularemia vaccine and 5

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were tularemia-naïve (control group). Nine of the 11 subjects received the skin test antigen on March 10, 1975. Two of the 11 subjects participated in a supplemental study and were challenged by intradermal (ID) route with skin test antigen approximately 3 weeks after the other 9 subjects were given the skin test. All subjects had blood tests and skin test monitoring.

A group of 12 healthy adult subjects from the professional staff at USAMRIID was to be tested; including 8 previously vaccinated with tularemia vaccine. Two of the 8 previously vaccinated were entered into a supplemental study to determine when the percent of A-RFC rose in the circulation of persons after ID challenge with the tularemia skin test antigen.

The remaining 4 subjects not previously vaccinated with tularemia vaccine were to serve as tularemia-naïve control subjects. The immune status of the subjects was to be confirmed by tularemia antibody titrations performed prior to the administration of the skin test. Subjects were to be in good health without symptoms of respiratory infection.

The study was to be conducted over an 18-day period, or longer if an individual subject's reaction warranted extended observation. The study was unblinded.

4 Exposure

The 3 routes of exposure for subjects enrolled in the studies supporting BB-IND 157 included (1) vaccination via multiple puncture technique, (2) aerosol, and (3) IC skin test.

Concomitant medications were not restricted in any study and many subjects were enrolled concurrently in other investigational protocols that exposed them to a variety of vaccines including smallpox, anthrax, yellow fever, and Q-fever. Likewise, subjects were not restricted from enrolling in multiple protocols that exposed them to a variety of investigational and licensed products offered as potential protection to infectious agents to which they might be exposed as part of their employment.

4.1 Vaccination via Multiple Puncture Technique

In most cases, a 5 mL vial containing 2 mL of lyophilized vaccine was reconstituted with 2 mL of Sterile Water for Injection, USP; however, two lots of TSI-GSD vaccine product (Lots 1R-85 and 2R-85) were packaged in 50 mL vials and were reconstituted with 20 mL of Sterile Water for Injection, USP. Regardless of vial size, the reconstitution process was identical.

To ensure homogeneous suspension, the reconstituted vial was shaken gently prior to administration of the vaccine. The area to be vaccinated was cleaned with acetone and allowed to air dry. A sterile needle was used to administer a droplet of vaccine product that was estimated to be approximately 0.1 mL. Once the vaccine was dropped onto the skin, a bifurcated needle was used to make 15 to 30 superficial punctures at the vaccination site to permit percutaneous (PC) penetration of the vaccine, (a process known as multiple puncture technique). Trace amounts of blood at the vaccination site were evidence of successful vaccine delivery.

After vaccination, the site was allowed to air dry for at least 5 minutes, then wiped with a dry, sterile gauze to remove any remaining vaccine. Vaccinated subjects were observed for approximately 30 minutes for signs of immediate hypersensitivity before they were released. Subjects were instructed to return for clinical examination at days specified in the protocol or upon any signs of infection (fever $>100.4^{\circ}\text{F}$ or pain at the injection site).

A "take" reaction, indicative of successful vaccination, was observed when the site of the vaccination progressed from a red papule to a vesicle to an eschar. An MA or a febrile agglutination (FA) titer $\geq 1:20$ (determined by the individual protocol) was considered a positive response.

4.2 Exposure via Respiratory Route

A modified Henderson apparatus with a Collision generator was used to provide the organisms via aerosol to subjects. Prior to exposure, the device was to be dismantled and autoclaved. The entire wing of Building 522 housing the apparatus was to be decontaminated by the Safety Division, U.S. Army Biological Laboratories (USABL) and tested for the presence of potential pathogens before use.

Human exposure was to be accomplished by a mask connected to the aerosol apparatus through a bypass valve. The valve allowed the subject to breathe filtered room air before, during, and after aerosol exposure. Opening and closing the valve was normally a function of the attending physician; however, the handle was accessible to the subject and he could decline exposure until the valve was opened and after exposure began. The procedure had the potential to be instantly terminated by the subject or the physician at any time. The apparatus worked under the relative humidity conditions of 80%; temperature 70°F.

Precautions for Use

Exposure to the aerosol apparatus and/or organisms was to be halted if any of the following occurred:

- 10 L inhaled as measured by the dry gas meter
- Exposure to aerosol for 90 seconds
- 18 respiratory cycles completed

Subjects exhibiting signs of tularemia disease after aerosol exposure were to be treated with 1 g streptomycin (intramuscular [IM] administration route) twice a day for 7 days at the discretion of the Project Ward Officer.

4.3 Exposure via Intracutaneous Route

The Foshay skin test antigen used in the single skin test study (Protocol 75-2) was a 1:1000 dilution of the phenol-killed tularemia vaccine first manufactured by Dr. Lee Foshay at the University of Cincinnati in 1943. The lot used for this study was delivered in 50 mL vacuum vials of lyophilized tularemia vaccine in May 1956 to the Chemical Corps Biological Laboratories, Fort Detrick, Frederick, Maryland (now known as USAMRIID). Between 1956 and 1974, 240 of 241 vials were used or discarded. One unopened vial was retained and contained lyophilized vaccine that had been refrigerated for 18 years at USAMRIID and restored to liquid form in 1973. Aliquots of this one 50 mL vial of Foshay tularemia vaccine were distributed under sterile conditions into glass containers. A larger aliquot, approximately 30 mL, was stored under sterile conditions at 4°C as the tularemia skin test stock antigen.

This skin test antigen had been used safely in over 1,000 persons at Fort Detrick and elsewhere. It was injected IC into the skin of the forearm in the same manner as a

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tuberculosis skin test. It was expected that subjects who had been vaccinated with tularemia vaccine would develop a positive reaction, consisting of reddening and induration (a firm elevation of the skin ≥ 0.5 cm) within 3 days at the skin test site. Itching and vesicle formation were also expected in some subjects who were more highly sensitive to the skin test antigen. More severe reactions, such as fever or abscess, or death of skin cells at the skin test site, had not been reported in persons who have been skin tested. The tularemia skin test reactions were expected to be no more frequent than reactions associated with a tuberculin tine test and were expected to disappear within several days to weeks.

5 Demographic and Baseline Data

5.1 Healthy Adult Subjects

Most study subjects were laboratory personnel at-risk of exposure to tularemia due to their employment. Subjects may have been selected from a pool of Medical Research Volunteer Subjects (MRVS) - a group of about 70 laboratory personnel who requested the opportunity to participate in clinical trials in lieu of combat - or may have been selected from a pool of volunteers enrolled in Project Whitecoat - young men, mostly members of the Seventh Day Adventist Church who elected to serve in the Armed Forces via noncombatant measures due to their religious convictions. Subjects in Project Whitecoat were well-informed about the risks of the studies. In an agreement between Seventh Day Adventist Church leaders and the Surgeon General of the Army, volunteers agreed to serve as research subjects in lieu of combat.

In total, there were 1,119 (88%) male and 151 (12%) female subjects, predominately white (85%) and between the ages of 20 and 29 (46%), enrolled in the tularemia clinical studies. Table 6 displays the demographic information for each study.

Table 6. Study Population Age, Race, and Gender Demographics by Protocol

Product:	NDBR 101						TSI-GSD 213		Aerosol Challenge		Skin Test	TOTAL
	11	4	2 and 4	4	3	4	2R-85/ 3-85	1R-85				
Lot:												
Study Number:	87-9 & 99-2 ¹	68-4/ 68-4A	65-8	65-7	65-4	AB-104	91-9	87-4	67-1	65-13/ 65-13A	75-2	
Number of Subjects:	N = 285	N = 20	N = 20	N = 12	N = 7	N = 720	N = 94	N = 69	N = 10	N = 22	N = 11	N = 1,270
Age (yrs)												
<19	-	-	1	-	-	24	-	4	-	-	-	29
20-29	59	19	19	6	3	357	32	59	10	22	2	588
30-39	93	1	-	4	2	120	47	6	-	-	6	279
40-49	84	-	-	2	2	140	15	-	-	-	1	244
50-59	41	-	-	-	-	57	-	-	-	-	2	100
60-69	5	-	-	-	-	16	-	-	-	-	-	21
over 70	-	-	-	-	-	-	-	-	-	-	-	0
no data	3	-	-	-	-	6	-	-	-	-	-	9
Race												
White	220	20	18	11	6	657	51	55	9	20	10	1,077
Black	14	-	2	1	1	49	38	9	1	2	-	117
Hispanic	2	-	-	-	-	-	1	5	-	-	-	8
Asian	11	-	-	-	-	-	3	-	-	-	-	14
Other	2	-	-	-	-	2	-	-	-	-	-	4
Unknown	36	-	-	-	-	12	1	-	-	-	1	50
Gender												
Male	223	20	20	12	6	665	72	59	10	22	10	1,119
Female	62	0	0	0	1	55	22	10	0	0	1	151

¹ Demographic information for studies 99-2 and 87-9 have been combined. Both studies vaccinated subjects with NDBR 101, Lot 11. Only 1 subject was enrolled in Protocol 99-2.

6 Definitions

Based on experience with previous lots of tularemia vaccine, it was expected that subjects would exhibit mild to moderate local reactions, such as low-grade pruritus and lymphadenopathy, and systemic reactions consisting of mild malaise, headache, myalgia, and arthralgia. It was also possible that an acute infection indistinguishable from the natural disease (along with modified forms of the natural disease) would occur, although animal studies had indicated the LVS strain contained in the study vaccine was less pathogenic than the fully virulent organism. Symptoms of the natural disease included fever, prostration, lymphadenopathy, hepatomegaly, splenomegaly, and fatigue lasting weeks to months after the infection if no treatment was given. For this reason, subjects who began to display symptoms of tularemia were to be treated with 1 g of streptomycin administered IM twice a day for 7 days. It was feared that failure to treat in a timely manner could result in a subject's death. Systemic allergic reactions and Guillain-Barré syndrome (GBS), an illness consisting of paralysis of the peripheral nerves in which there is numbness and weakness in the limbs that is usually reversible, were also possible severe reactions, although they were not expected.

The Principal Investigator (PI), along with nursing staff and a standard emergency kit (crash cart), was available during the observation period in the event of a local or systemic adverse reaction immediately following vaccination.

In the vaccination studies (Protocols 99-2, 87-9, 68-4/68-4A, 65-8, 65-7, 65-4, AB-104, 91-9, and 87-4), safety was monitored by direct physical examination, vital signs (including temperature, blood pressure, and pulse), measurement of the presence of local reactions at the site of vaccination, and/or AE reporting.

In the aerosol challenge studies (Protocols 67-1 and 65-13/65-13A), safety was measured by the frequency, severity, and relationship of adverse reactions, selected laboratory tests outside the established reference range, throat cultures, vital signs, alterations in blood chemistry, and/or metabolism. The level of protection afforded vaccinated and unvaccinated subjects against aerosol exposure of *F. tularensis* was assessed in this study by evaluating safety parameters of temperature, pulse, and post challenge AEs (PEs).

In the skin test study (Protocol 75-2), safety was evaluated solely by laboratory values outside of an established reference range.

6.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational drug (vaccine) that does not necessarily have a causal relationship with this treatment. An AE, therefore, can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease

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temporally associated with the use of an investigational product (e.g., tularemia vaccine, aerosol, or skin test antigen) whether or not causally related.

A serious adverse event (SAE) is any untoward medical occurrence that results in any of the following outcomes:

1. death
2. life-threatening AE
3. inpatient hospitalization or prolongation of existing hospitalization
4. persistent or significant disability/incapacitation
5. congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. AEs to the vaccine, aerosol, or skin test antigen were to be recorded by study personnel on the laboratory, clinical, or microbiological data collection form located in the subject's study record, as they were reported. An Adverse Reaction Report (Form FDA 1639), the precursor to the MedWatch or Vaccine Adverse Event Reporting System (VAERS) form used in present-day studies, would most likely have been used to report any SAEs.

An unexpected AE is an adverse reaction, the nature or severity of which is not consistent with the applicable product information or any AE that has not been documented previously as an event to be expected (i.e., nature, frequency, or intensity) with administration of the test article.

AEs reported here are a compilation of AEs as reported in the final integrated clinical and statistical reports for BB-IND 157, regardless of the route of exposure to tularemia. Note that at the time the study was conducted, the term "PE" (postexposure event) was used to describe AEs that occurred after subjects were exposed to an aerosol challenge. PEs are still AEs, but more specifically relate to the timing of the AE. More detailed information concerning the reported AEs may be found in the individual Final Integrated Clinical and Statistical Report, submitted to the FDA.

6.2 Severity

The severity of local and systemic reactions was assessed according to the criteria in Tables 7 and 8, respectively. The assessment was made during a retrospective review of medical records conducted by the Medical Reviewer, Dr. Patricia Pettit.

Table 7. Criteria for Rating Local Reactions to Tularemia Exposure

Category	Criteria
<i>Mild</i>	L⁰ - No reaction or erythema only; no limitations on measurement are applicable to the extent of the erythema. L¹ - Edema/Induration, usually with erythema (but need not be present), measuring 3-30 mm inclusive in either of two diameters. L² - Edema/Induration, usually with erythema (but need not be present), measuring 31 to 60 mm inclusive in either of two diameters.
<i>Moderate</i>	L³ - Edema/Induration, usually with erythema (but need not be present), measuring 61 to 120 mm inclusive in either of two diameters. L⁴ - Edema/Induration, with or without erythema, >120 mm in either diameter. When the area of edema/induration involves the elbow, forearm, wrist, or clavicular fossa, notation was made of the areas involved.
<i>Severe</i>	L⁵ - Edema/Induration same as in L⁴ with marked limitation of normal use of the area with axillary node tenderness. L⁶ - Any local reaction (irrespective of extent of edema/induration or erythema) that is accompanied by cyst or abscess formation or by necrosis with or without dermal slough. L^N - Special category for firm or "rubbery" indurated/nodular areas located deep subcutaneously or IM at injection site persisting beyond the usual 48-hour observation period.

Note: Measurements are made in two diameters perpendicular to each other.

Table 8. Criteria for Rating Systemic Reactions to Tularemia Exposure

Ranking	Systemic Reaction Characterized by 3 or More of the Following:
<i>Mild</i>	Mild headache (no analgesics required) Mild generalized muscle and joint aches (no analgesics) Mild chilly sensation Slight loss of appetite Slight nausea Fever 98.8° to 99.6°F
<i>Moderate</i>	Headache, repeated and persistent (relieved by analgesics) Generalized, persistent muscle and joint aches relieved by analgesics Moderate, repeated chills with mild sweats Moderate feverishness Moderate loss of appetite Nausea, persistent but without vomiting Fever >99.6° to 101°F
<i>Severe (marked)</i>	Headache, unrelieved or only partially relieved with analgesics Complete loss of initiative or energy Generalized muscle or joint pain only partially relieved by analgesics Repeated shaking chills Profuse sweats, requiring change of clothing Pronounced and persistent nausea accompanied by vomiting Diarrhea Fever >101°F

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6.3 Causal Relationship

Using the following criteria, the Medical Reviewer assessed the relationship of the AEs to the administration of the vaccine, aerosol, or skin test antigen.

Definitely/Certainly Related: Events occurring within a timely manner after administration of the vaccine, aerosol, or skin test antigen that are known sequelae to the administration of the vaccine, aerosol, or skin test antigen and follow a previously documented pattern of reaction but for which no other explanation is known. This category applies to AEs the investigator believes are incontrovertibly related to the vaccine, aerosol, or skin test antigen.

Probably Related: Any event occurring in a timely manner after administration of the vaccine, aerosol, or skin test antigen that follows a known pattern of reaction to the vaccine, aerosol, or skin test antigen and for which no other explanation is known. This category applies to AEs that, after careful medical consideration at the time they are evaluated, are believed with a high degree of certainty to be related to the vaccine, aerosol, or skin test antigen.

Possibly Related: Any event occurring in a timely manner after administration of the vaccine, aerosol, or skin test antigen that does not follow a known pattern of reaction and for which no other explanation is known. This category applies to AEs that, after careful medical consideration at the time they are evaluated, are considered unlikely to be related but cannot be ruled out with certainty.

Unrelated/Unlikely Related: In general, this category can be considered applicable to AEs that, after careful medical consideration at the time they are evaluated, are considered to be unrelated to administration of the vaccine, aerosol, or skin test antigen.

Not Related: Any AE for which there is evidence that an alternative etiology exists or for which no timely relationship exists to the administration of the vaccine, aerosol, or skin test antigen and the AE does not follow any previously documented pattern. This category applies to AEs that, after careful medical consideration, are clearly and incontrovertibly due to causes other than the vaccine, aerosol, or skin test antigen.

Unclassifiable: Any AE for which there is insufficient information to allow for an assessment of causality.

6.4 Laboratory Values of Particular Interest

Common LFTs are of particular interest and four of the clinical trials, specifically Protocols 87-9, 68-4/68-4A, 91-9, and 87-4, made it a point to investigate ALT and AST levels that were out-of-reference range. These LFTs are being defined as "laboratory values of particular interest" for the purpose of this report and more detail is given in Section 9.1 (Summary of Elevated Transaminase Findings) of this integrated summary.

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7 Methods

7.1 Data Coding and Validation

Data were collected and managed via the subject's study record. The study data were entered in a computerized database, verified against subject study records, and transferred to SAS format for statistical analysis and for FDA submission using SAS version 8.2. None of the studies was formally monitored.

It should be noted that laboratory reference ranges from many of the studies were not available; therefore, reference ranges from a subsequent study (Protocol 87-4) may have been used as a surrogate.

It is unknown whether formal quality assurance or control systems other than SOPs were in place at the time of the study.

8 Adverse Events Reported During Clinical Trials

8.1 Summary of Adverse Event Experience

There was great variability in data collection methods among the studies and study personnel. AEs were to be recorded on the laboratory, clinical, or microbiological data collection form located in the subject's study record, as they were reported; however, there was no standard case report form. Therefore, AEs were often inconsistently reported. Likewise, AEs were not routinely collected on every subject at the prescribed time points as instructed in the protocol. Some AEs were expected to occur (i.e., lesion, fever, erythema, induration, "take" reaction) and were not consistently recorded.

Subjects may have experienced more than one AE and the same AE may have occurred more than once; however, in subjects with multiple observations of the same AE, only the highest severity rating was used.

There were 1,119 AEs reported among the 1,270 subjects enrolled in the 12 studies. The percentages of AEs reported among the NDBR 101 and TSI-GSD 213 products appear to be relatively equal (42% vs. 44%, respectively, across all studies); however, there were substantially more subjects in the NDBR 101 studies than the TSI-GSD 213 studies (1,064 vs. 163, respectively). There were 468 AEs reported among the 1,064 subjects vaccinated by an NDBR 101 product and 493 AEs reported among the 163 subjects vaccinated by a TSI-GSD 213 product. The smaller number of AEs reported in the NDBR 101 studies may be because the NDBR 101 product was less reactogenic than the TSI-GSD 213 product or because data collection methods were more thorough in the TSI-GSD 213 studies. The TSI-GSD 213 studies were conducted for the most part after the NDBR 101 studies when more reporting guidance became more stringent (i.e., Good Clinical Practices).

There were 158 AEs reported among the 32 subjects in the aerosol challenge studies accounting for 14% of the total number of AEs reported across all studies. No AEs were reported by subjects in the skin test study. Table 9 shows the itemization of AEs by Body System for each route of tularemia exposure.

Table 9. AEs Recorded by Body System for Each Route of Tularemia Exposure

Adverse Events Recorded:	NDBR 101 Product Studies (N=1,064)	TSI-GSD 213 Product Studies (N=163)	Aerosol Challenge Studies (N=32)	Skin Test Study (N=11)	Total (N=1,270)
Body System					
Body as a Whole	85	68	82	0	235
Cardiovascular	0	0	0	0	0
Digestive	0	4	0	0	4
Eyes, Ears, Nose, Throat	7	6	31	0	44
Gastrointestinal	5	27	7	0	39
Hemic & Lymphatic	54	35	0	0	89
Metabolic & Nutritional	0	0	0	0	0
Musculoskeletal	17	28	25	0	70
Nervous System	4	6	3	0	13
Respiratory	1	20	6	0	27
Skin & Appendages	295	298	4	0	597
Urogenital	0	1	0	0	1
Total (percent of total)	468 (42%)	493 (44%)	158 (14%)	0 (0%)	1,119 (100%)

N=Number of Subjects

The safety profile of the tularemia vaccine is mainly characterized by typical vaccination reactions. Of the 12 body systems, 53% of the AEs were in the Skin and Appendages body system with papule (13%), lesion and lesion at injection site (11%), and pruritus (7%) being the top 3 AEs reported. AEs in the Body as a Whole, Hemic and Lymphatic, and Musculoskeletal body systems accounted for 21%, 8%, and 6.3%, respectively, with the top AEs reported being headache (7.4%), fever (4.7%), malaise (4.7%), lymphadenopathy (8%), and myalgia (4.4%). The remaining 8 body systems accounted for less than 12% of the recorded AEs: Cardiovascular (no AEs reported), Digestive (0.4%), Eyes, Ears, Nose, Throat (4%), Gastrointestinal (3.5%), Metabolic and Nutritional (no AEs reported), Nervous (1.2%), Respiratory (2.4%), and Urogenital (0.1%).

There were no gender or age differences in any of the studies when AEs were compared, nor were there any site differences as AEs reported from multiple sites may have been combined in the analysis.

Table 10 lists the AEs reported from each study, by body system. A description of AEs reported during each study follows the table.

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Table 10. Adverse Events Reported for Each Study, by Body System (continued)

Product:	NDBR 101					TSI-GSD 213		Aerosol Challenge		Skin Test	
	11	4	2/4	4	3	4	2R-85/ 3-85				
Lot:	87-9 & 99-2 ¹	68-4/ 68-4A ²	65-8	65-7	65-4	AB-104	91-9	87-4 ³	67-1	65-13/ 65-13A ⁴	TOTAL
Number of Subjects (N):	285	20	20	12	7	720	94	69	10	22	1,270
Cardiovascular	0	0	0	0	0	0	0	0	0	0	0
None reported											-
Digestive	0	0	0	0	0	0	4	0	0	0	4
Diarrhea							4				4
Eyes, Ears, Nose, Throat	0	0	0	0	0	0	0	6	6	13	44
Allergic rhinitis								2			2
Aphthous ulcers										1	1
Conjunctival diffusion										1	1
Conjunctival injection		1	1							5	12
Conjunctivitis								1			1
Coryza										1	3
Eyes burning										1	1
Ocular pain										1	1
Otitis externa										1	1
Pharyngeal injection										1	8
Photophobia		1							6		2
Retro-orbital pain		2									3
Rhinorrhea								1		1	1

¹ Information for studies 99-2 and 87-9 have been combined; both studies vaccinated subjects with NDBR 101, Lot 11. Only 1 subject was enrolled in Protocol 99-2 and reported no AEs.

² First number represents AEs postvaccination; second number represents AEs for unvaccinated controls after aerosol challenge; third number represents AEs for vaccinated subjects after aerosol challenge.

³ Product vs. placebo. Only AEs associated with product are reported here.

⁴ Number represents total AEs reported for all subjects (regardless of lot received or level of dose challenge).

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Table 10. Adverse Events Reported for Each Study, by Body System (continued)

Product:	NDBR 101					TSI-GSD 213		Aerosol Challenge	Skin Test
	11	4	2/4	4	3	4	2R-85/ 3-85	1R-85	
Lot:	11	4	2/4	4	3	4			
Study Number:	87-9 & 99-2 ¹	68-4/ 68-4A ²	65-8	65-7	65-4	AB-104	91-9	87-4 ³	65-13/ 65-13A ⁴
Number of Subjects (N):	285	20	20	12	7	720	94	69	67-1
Eyes, Ears, Nose, Throat (cont.)									
Sore throat		2							1
Tinnitus									2
Toothache								1	
Gastrointestinal	2	0	0	3	0	0	8	19	3
Abdominal distention									3
Abdominal pain									1
Diarrhea		1						4	
Elevated liver function tests							2	5	1
Emesis		1					1		
GI upset	1						2	1	
Hiccups								1	
Nausea	1	1					3	2	3
									2
									12
									7
									2
									4
									1
									1
									5
									1
									1
									39
									1
									4
									8
									7
									2
									4
									1
									12

¹ Information for studies 99-2 and 87-9 have been combined; both studies vaccinated subjects with NDBR 101, Lot 11. Only 1 subject was enrolled in Protocol 99-2 and reported no AEs.

² First number represents AEs postvaccination; second number represents AEs for unvaccinated controls after aerosol challenge; third number represents AEs for vaccinated subjects after aerosol challenge.

³ Product vs. placebo. Only AEs associated with product are reported here.

⁴ Number represents total AEs reported for all subjects (regardless of lot received or level of dose challenge).

Table 10. Adverse Events Reported for Each Study, by Body System (continued)

Table 10. Adverse Events Reported for Each Study, by Body System (continued)														
Product:		NDBR 101						TSI-GSD 213		Aerosol Challenge		Skin Test		
Lot:	11	4	2/4	4	3	4	2R-85/ 3-85	1R-85	67-1	65-13/ 65-13A ⁴	75-2			
Study Number:	87-9 & 99-2 ¹	68-4/ 68-4A ²	65-8	65-7	65-4	AB-104	91-9	87-4 ³			TOTAL			
Number of Subjects (N):	285	20	20	12	7	720	94	69	10	22	11	1270		
Hemic & Lymphatic	9	10	14	9	5	7	22	13	0	0	0	89		
Congested vessels								1				1		
Lymphadenopathy	9	10	14	9	5	7	22	11				87		
Splenomegaly								1				1		
Metabolic & Nutritional Disorders	0	0	0	0	0	0	0	0	0	0	0	0		
None reported	-	-	-	-	-	-	-	-	-	-	-	-		
Musculoskeletal	6	0	0	0	0	3	13	15	9	13	3	70		
Arthralgia	1						4	1				6		
Back pain		1	1			1	1	2	2	2		9		
Joint pain								2				3		
Knee pain								1				1		
Muscle strain	1											1		
Myalgia	3	2	4			2	8	9	7	11	3	49		
Shoulder strain	1											1		
Nervous	4	0	0	0	0	0	2	4	0	3	0	13		
Dizziness	2						1	4		1		8		
Lethargic										1		1		
Only 1 subject was enrolled in Protocol														

¹ Information for studies 99-2 and 87-9 have been combined; both studies vaccinated subjects with NDBR 101, Lot 11. Only 1 subject was enrolled in Protocol 99-2 and reported no AEs.

² First number represents AEs postvaccination; second number represents AEs for unvaccinated controls after aerosol challenge; third number represents AEs for vaccinated subjects after aerosol challenge.

³ Product vs. placebo. Only AEs associated with product are reported here.

⁴ Number represents total AEs reported for all subjects (regardless of lot received or level of dose challenge).

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Table 10. Adverse Events Reported for Each Study, by Body System (continued)

Product:	NDBR 101							TSI-GSD 213		Aerosol Challenge		Skin Test
	Lot:	11	4	2/4	4	3	4	2R-85/ 3-85	1R-85	67-1	65-13/ 65-13A ⁴	
Study Number:	87-9 & 99-2 ¹	68-4/ 68-4A ²	65-8	65-7	65-4	AB-104	91-9	87-4 ³				TOTAL
Number of Subjects (N):	285	20	20	12	7	720	94	69	10	22	11	1,270
Nervous (cont.)												
Numbness										1		1
Paresthesia	2						1					3
Respiratory	1	0	0	0	0	0	15	5	0	5	1	27
Chest infiltrates										1		1
Congestion							4	1				5
Cough							1	3		2		6
Pneumonitis										1		1
Rales										1		1
Rhinorrhea							4					4
Sinusitis	1											1
Sore throat							6					6
URI symptoms								1		1		2
Skin & Appendages	36	86	0	0	41	30	174	124	1	3	0	597
Blister						1						1
Contact dermatitis								1				1
Dermatitis								1				1
Erythema	2	19	3	2	2	4		17				49

Only 1 subject was enrolled in Protocol

Erythema	Z	19
¹ Information for studies 99-2 and 87-9 have been combined; both studies vaccinated subjects with NDBR 101, Lot 11. Only 1 subject was enrolled in Protocol 99-2 and reported no AEs.		

2 First number represents AEs postvaccination; second number represents AEs for unvaccinated controls after aerosol challenge; third number represents AEs for vaccinated subjects after aerosol challenge.

3. Reactivity to products. Only AEs associated with product are reported here.

³ Product vs. placebo. Only AEs associated with product are reported here.

⁴ Number represents total AEs reported for all subjects (regardless of lot received or level of dose challenge).

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Table 10. Adverse Events Reported for Each Study, by Body System (continued)

Table 10. Adverse Events Reported for Each Study, by Body System (continued)																
Product:		NDBR 101										TSI-GSD 213		Aerosol Challenge		Skin Test
Lot:		11	4	2/4	4	3	4	2R-85/ 3-85	1R-85	67-1		65-13/ 65-13A ⁴				
Study Number:	87-9 & 99-2 ¹	68-4/ 68-4A ²	65-8	65-7	65-4	AB-104	91-9	87-4 ³					75-2	TOTAL		
Number of Subjects (N):	285	20	20	12	7	720	94	69	10	22			11	1,270		
Skin & Appendages (cont.)																
Eschar						1								1		
Folliculitis										1				1		
Induration	1	17		2		2		13						35		
Keloid								1						1		
Lesion	13	20			7	50	6							96		
Lesion (injection site)								31						31		
Macule	1		19	6				7						33		
Maculopapule				8	7									15		
Palpebra pruritus	1													1		
Papule	4		19	11	5	6	91	9						145		
Pruritus	2	13		1	3	8	35	17						79		
Pustule	5	2			1		34	6						48		
Rash	4						2	3	1	2				12		
Sterile abscess								1						1		
Swollen eyelids	1													1		
Tenderness		7				1		10						18		
Tinea cruris								1						1		

Only 1 subject was enrolled in Protocol

¹ Information for studies 99-2 and 87-9 have been combined; both studies vaccinated subjects with NDBR 101, Lot 11. Only 1 subject was enrolled in Protocol 99-2 and reported no AEs.

² First number represents AEs postvaccination; second number represents AEs for unvaccinated controls after aerosol challenge; third number represents AEs for vaccinated subjects after aerosol challenge.

³ Product vs. placebo. Only AEs associated with product are reported here.

⁴ Number represents total AEs reported for all subjects (regardless of lot received or level of dose challenge).

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Table 10. Adverse Events Reported for Each Study, by Body System (continued)

Table 10. Adverse Events Reported for Each Study, by Body System (continued)												
Product:		NDBR 101						TSI-GSD 213		Aerosol Challenge		Skin Test
Lot:	11	4	2/4	4	3	4	2R-85/ 3-85	1R-85				
Study Number:	87-9 & 99-2 ¹	68-4/ 68-4A ²	65-8	65-7	65-4	AB-104	91-9	87-4 ³	67-1	65-13/ 65-13A ⁴	75-2	TOTAL
Number of Subjects (N):	285	20	20	12	7	720	94	69	10	22	11	1,270
Skin & Appendages (cont.)												
Ulcer								1				1
Vesicle	2	8			3	1	6	5				25
Urogenital	0	0	0	0	0	0	1	0	0	0	0	1
Pyuria							1					1
TOTAL	93	99	22	36	55	90	273	220	45	77	37	1,119
Only 1 subject was enrolled in Protocol												

¹ Information for studies 99-2 and 87-9 have been combined; both studies vaccinated subjects with NDBR 101, Lot 11. Only 1 subject was enrolled in Protocol 99-2 and reported no AEs.

² First number represents AEs postvaccination; second number represents AEs for unvaccinated controls after aerosol challenge; third number represents AEs for vaccinated subjects after aerosol challenge.

³ Product vs. placebo. Only AEs associated with product are reported here.

⁴ Number represents total AEs reported for all subjects (regardless of lot received or level of dose challenge).

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8.2 NDBR 101 Safety

8.2.1 Protocol 99-2, Log A-8573: A Longitudinal Phase 2 Multi-Site Study for the Continued Evaluation of the Safety and Immunogenicity of a Live *Francisella tularensis* Vaccine, NDBR 101

No AEs were reported in this study that vaccinated one subject with NDBR 101, Lot 11.

8.2.2 Protocol 87-9, Log A-4707: Evaluation of New Lots of Tularemia Vaccine, Protocol B: Comparative Assessment of *Francisella tularensis* Vaccine, Live, TSI-GSD 213 Lot 1R, and *Francisella tularensis* Vaccine, Live, NDBR 101 Lot 11

Study data show the majority of the 93 AEs from primary vaccination were reported within the first 3 days of inoculation, and all AEs resolved without sequelae. A total of 297 doses of vaccine were administered to 284 subjects. No AE data were documented for 128 vaccinations.

Of those subjects reporting AEs after the primary vaccination from Lot 11, 13 subjects reported erythematous, papular lesions typically associated with vaccination, which resolved spontaneously. Pustules developed in 5 of 156 subjects and healed within 2 weeks. These papular lesions were an expected occurrence of the vaccination and therefore were considered to be related to the vaccine.

The most commonly reported AEs were lesions (13 subjects), malaise (12 subjects), headache (11 subjects), lymphadenopathy (9 subjects), and fever (6 subjects). Lesions were only recorded for subjects who were enrolled in the study at extramural locations. USAMRIID did not use this category in its AE reporting because erythematous, papular lesions were typical of vaccination and considered an expected event.

There were no location (USAMRIID vs. extramural sites) differences in AE rates following primary vaccination, except for reported lesions, which was a category not used at USAMRIID. Mean ages were slightly higher for those having reactions but could not be evaluated using statistical methods due to the sparse number of reactions. There was no gender effect on AE rates. Few AEs were severe (1 headache, 1 pain). Overall AE rates pooled over gender and location varied from 0.6% to a maximum of 8.1% (lesion, extramural only) for the primary vaccination (Table 11).

Table 11. Adverse Events Pooled over Location, Gender, Days, and Site (excluding records of vaccinations without recorded AEs) (Protocol 87-9, Lot 11) by Body System

Event	N of AEs	% of Subjects	Days Post Vaccination				Site	
			1-3 days	4-7 days	8-14 days	≥15 days	USAMRIID (64 doses)	Extra-mural (96 doses)
Body as a Whole								
Chest pain	1	0.6	1	-	-	-	1	0
Fatigue	3	1.9	1	1	-	1	2	1
Fever	6	3.8	6	-	-	-	2	4
Headache	11	6.9	7	-	1	3	3	8
Malaise	12	7.5	7	1	2	2	2	10
Pain	2	1.3	2	-	-	-	1	1
Cardiovascular								
None reported								
Digestive								
None reported								
Eyes, Ears, Nose, Throat								
None reported								
Gastrointestinal								
GI upset	1	0.6	-	-	1	-	1	0
Nausea	1	0.6	1	-	-	-	1	0
Hemic and Lymphatic								
Lymphadenopathy	9	5.6	2	1	1	5	3	6
Metabolic & Nutritional Disorders								
None reported								
Musculoskeletal								
Arthralgia	1	0.6	1	-	-	-	0	1
Muscle strain	1	0.6	1	-	-	-	1	0
Myalgia	3	1.9	1	-	2	-	1	2
Shoulder strain	1	0.6	1	-	-	-	1	0
Nervous System								
Dizziness	2	1.3	2	-	-	-	1	1
Paresthesia	2	1.3	1	1	-	-	2	0
Respiratory								
Sinusitis	1	0.6	-	-	1	-	1	0

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Table 11. Adverse Events Pooled over Location, Gender, Days, and Site (excluding records of vaccinations without recorded AEs) (Protocol 87-9, Lot 11) by Body System (continued)

Event	N of AEs	% of Subjects	Days Post Vaccination				Site	
			1-3 days	4-7 days	8-14 days	≥15 days	USAMRIID (64 doses)	Extra-mural (96 doses)
Skin and Appendages								
Erythema	2	1.3	1	-	-	1	0	2
Induration	1	0.6	1	-	-	-	1	0
Lesion	13	8.1	11	-	-	2	2	11
Macule	1	0.6	1	-	-	-	0	1
Palpebra pruritus	1	0.6	1	-	-	-	1	0
Papule	4	2.5	4	-	-	-	0	4
Pruritus	2	1.3	1	-	1	-	2	0
Pustule	5	3.1	3	2	-	-	2	3
Rash	4	2.5	-	3	-	1	1	3
Swollen eyelids	1	0.6	-	1	-	-	1	0
Vesicle	2	1.3	1	1	-	-	0	2
Total	93		58	11	9	15	33	60

Many of the subjects reporting AEs were enrolled in multiple protocols that exposed them to a variety of investigational and licensed products offered as potential protection to infectious agents to which they might be exposed to as part of their employment. Preliminary analysis of the AE data from those subjects enrolled in multiple protocols did not indicate a higher rate of AEs reported versus data from those subjects who were not enrolled in multiple protocols; however, on April 2, 2002, an SAE was reported for a 31-year-old white male who was vaccinated from Lot 11 on December 10, 1998, at USAMRIID. The subject reported pain and a loss of vision in his right eye and was subsequently evaluated as an outpatient in a hospital emergency room and referred to an eye specialty clinic for follow-up. The subject was evaluated and treated with prednisone and acetate (1%) eye drops. The SAE report states that the subject was enrolled and participated in seven other investigational studies that included Venezuelan Equine Encephalomyelitis Virus Vaccine (2 studies), Eastern Equine Encephalomyelitis Vaccine, Q-Fever Vaccine, Western Equine Encephalitis Vaccine, Botulinum Vaccine, and Anthrax Vaccine. The subject had also received a licensed smallpox vaccine.

The initial safety report (Serial #117, August 8, 2002) stated that the subject's autoimmune condition (HLA-B27-associated uveitis) could have been further aggravated by these multiple vaccinations; however, further investigation, including a consultation with the treating ophthalmologist, led to the determination that causality between the SAE and the subject receiving multiple vaccinations was unlikely since the subject was predisposed to uveitis due to an autoimmune condition. Although HLA-B27-associated

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autoimmune disease is considered chronic, improvement in uveitis was seen after treatment, with normal vision returning. The last follow-up visit for this subject under this protocol was June 28, 2002, and the subject is no longer enrolled in this study. An updated safety report was submitted to FDA on January 29, 2003 (Serial #125). This is the only subject enrolled in this protocol for whom a safety report was submitted.

8.2.3 Protocol 68-4 and 68-4A: Evaluation of Storage Stability of Tularemia Vaccine, Live, Attenuated NDBR 101, Lot 4

The frequency, severity, and relationship of adverse reactions to NDBR 101, Lot 4 were recorded in each subject's hospital record and monitored. AEs were expected and, due to the small study population, not further evaluated. AE and PE rates were tabulated for each reaction and mean ages were computed for each AE (present or absent), but no discernible age trend was apparent. No deaths were reported during either part of this study. **Note that at the time the study was conducted, the term "PE" was used to describe AEs that occurred after subjects were exposed to an aerosol challenge. PEs are still AEs, but more specifically relate to the timing of the AE.**

Part I - Immunization

All 20 subjects developed a small (less than 1 cm) erythematous maculopapular lesion. Ninety-nine (99) AEs were reported and included induration (17 subjects), pruritus (13 subjects), lymphadenopathy (10 subjects), vesicle (8 subjects), local tenderness (7 subjects), and pustule (2 subjects). Table 12 lists the frequency of AEs reported in Part I, by body system.

Table 12. Frequency of AEs Reported by Body System (Protocol 68-4, NDBR 101, Lot 4)

Event	Lot 4	
	N of AEs	% of Subjects
Body as a Whole		
Headache	3	15
Cardiovascular		
None reported		
Digestive		
None reported		
Eyes, Ears, Nose, Throat		
None reported	-	-
Gastrointestinal		
None reported	-	-
Hemic and Lymphatic		
Lymphadenopathy	10	50
Metabolic & Nutritional Disorders		
None reported		

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Table 12. Frequency of AEs Reported by Body System (Protocol 68-4, NDBR 101, Lot 4) (continued)

Event	Lot 4	
	N of AEs	% of Subjects
Musculoskeletal		
None reported	-	-
Nervous System		
None reported	-	-
Respiratory		
None reported	-	-
Skin and Appendages		
Erythema	19	95
Induration	17	85
Lesion	20	100
Pruritus	13	65
Pustule	2	10
Tenderness	7	35
Vesicle	8	40
Total AEs	99	

All AEs were either mild (84%) or moderate (14%) in severity (one AE was not graded). No AEs were graded as severe, nor were any SAEs reported. All reactions resolved without sequelae.

Part II - Aerosol Challenge

A total of 58 PEs were recorded, 16 from Group 1 (low-dose challenge) and 42 from Group 2 (high-dose challenge). Four vaccinated subjects from Group 1 (25%) reported no PEs. Rates of PEs between vaccinated and control subjects were compared by Fisher's exact test adjusted for multiple comparisons. Since the vaccine and control groups were balanced with respect to exposure to low- and high-dose challenge, the challenge groups were combined to obtain statistical power for the test.

The most common PEs reported by vaccinated, challenged subjects (Group 1 and Group 2 combined) were headache (9 subjects), malaise (4 subjects), myalgia (4 subjects), anorexia (3 subjects), and fever (3 subjects). The most common PEs reported by unvaccinated control subjects were fever (4 subjects), headache (4 subjects), anorexia (3 subjects), chest pain (3 subjects), malaise (3 subjects), and myalgia (2 subjects).

The majority of subjects reported headache, with no statistical significance between the groups (9 vaccinated subjects vs. 4 control subjects; $p = 0.681$). Three severe PEs were reported, all in Group 2 (1 vaccinated subject reported a severe headache; 1 control subject reported a severe headache and back pain). No serious PEs were reported in

Group 2 for either control or vaccinated subjects. Table 13 illustrates the group comparison of reported PEs.

Table 13. Group Comparison of PEs Reported, by Body System, Pooled Challenge Dose

Event	Unvaccinated Controls Groups 1 & 2 (pooled)		Vaccinated Groups 1 & 2 (pooled)		p value
	N = 4	% of Subjects	N = 16	% of Subjects	
Body as a Whole					
Anorexia	3	75	3	18.8	0.061
Chest pain	3	75	1	6.3	0.013
Fever	4	100	6	37.5	0.087
Headache	4	100	9	56.3	0.249
Malaise	3	75	4	25	0.101
Eyes, Ears, Nose, Throat					
Conjunctival Inject	1	25	1	6.3	0.368
Photophobia	1	25	-	-	0.200
Retro-orbital pain	-	-	2	12.5	1.000
Sore throat	-	-	2	12.5	1.000
Cardiovascular					
None reported	-	-	-	-	-
Digestive					
None reported	-	-	-	-	-
Eyes, Ears, Nose, Throat					
None reported	-	-	-	-	-
Gastrointestinal					
Diarrhea	-	-	1	6.3	1.000
Emesis	-	-	1	6.3	1.000
Nausea	-	-	1	6.3	1.000
Hemic and Lymphatic					
None reported	-	-	-	-	-
Metabolic & Nutritional Disorders					
None reported	-	-	-	-	-
Musculoskeletal					
Back pain	1	25	1	6.3	0.368
Myalgia	2	50	4	25	0.549
Nervous System					
None reported	-	-	-	-	-
Respiratory					
None reported	-	-	-	-	-

N = Number of subjects

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Table 13. Group Comparison of PEs Reported, by Body System, Pooled Challenge Dose (continued)

Event	Unvaccinated Controls Groups 1 & 2 (pooled)		Vaccinated Groups 1 & 2 (pooled)		p value
	N = 4	% of Subjects	N = 16	% of Subjects	
Skin and Appendages					
None reported	-	-	-	-	-
Total PEs	22		36		

N = Number of subjects

Five of 6 subjects reporting fever and 1 subject reporting chest pain were from the high-dose challenge group. None of the 4 subjects in the low-dose challenge group reported PEs. Other than headache, only 1 case of malaise and 1 of fever were reported in the low-dose challenge group of vaccinated subjects, whereas numerous clinical reactions were reported by vaccinated subjects in the high-dose challenge group.

Five cases of fever in the vaccinated subjects exposed to high-dose challenge compare to 1 case of fever in the low-dose challenge group. Although this difference is not statistically significant by Fisher's exact test ($p = 0.12$), it is highly suggestive of a breakthrough when placed in context with the other reactions. In addition, one case of infection required antibiotic intervention in the vaccinated subjects exposed to high-dose challenge; no cases of infection requiring antibiotic intervention in the vaccinated subjects exposed to low-dose challenge. All control subjects in the low-dose and high-dose challenge groups ($N = 4$) required antibiotic intervention.

The majority (87.5%) of PEs reported by all subjects in Group 1 and 81% of PEs reported by subjects in Group 2 were either mild or there were no data to make a determination. No SAEs were reported by either group.

8.2.4 Protocol 65-8: Evaluation of Attenuated Tularemia Vaccine (LVS) from National Drug [Biologic Research] Company

All 20 subjects developed a small (less than 1 cm) erythematous maculopapular lesion at the site of vaccination. Fifty-five (55) AEs were reported and included lymphadenopathy (7 subjects vaccinated with Lot 2, 7 subjects vaccinated with Lot 4), macule (9 subjects vaccinated with Lot 2, 10 subjects vaccinated with Lot 4), papule (9 subjects vaccinated with Lot 2, 10 subjects vaccinated with Lot 4), and erythema (1 subject vaccinated with Lot 2, 2 subjects vaccinated with Lot 4). AE rates were tabulated for each reaction, and mean ages were computed for each AE (present or absent), but no discernible age trend was apparent. Table 14 lists the frequency of AEs reported by body system.

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Table 14. Frequency of AEs Reported by Body System

Event	Lot 2 (N = 10)		Lot 4 (N = 10)	
	Number of AEs	% of Subjects	Number of AEs	% of Subjects
Body as a Whole				
None reported	-	-	-	-
Cardiovascular				
None reported	-	-	-	-
Digestive				
None reported	-	-	-	-
Eyes, Ears, Nose, Throat				
None reported	-	-	-	-
Gastrointestinal				
None reported	-	-	-	-
Hemic and Lymphatic				
Lymphadenopathy	7	70	7	70
Metabolic & Nutritional Disorders				
None reported	-	-	-	-
Musculoskeletal				
None reported	-	-	-	-
Nervous System				
None reported	-	-	-	-
Respiratory				
None reported	-	-	-	-
Skin and Appendages				
Erythema	1	10	2	20
Macule	9	90	10	100
Papule	9	90	10	100
Total AEs (55)	26		29	

All AEs occurred within 7 days postvaccination with the exception of papule and maculopapule, which occurred between Days 8 and 14 and resolved without known sequelae. No subjects developed an actual or modified form of the natural disease, systemic allergic reaction, or GBS.

Upon review of the subjects' study records, the Medical Reviewer graded all AEs (for which data were available for review) as mild. All but one AE reported by a Lot 2 subject were judged by the Medical Reviewer to be definitely related to the vaccine; the remaining AE (lymphadenopathy) was judged to be probably related to the vaccine. All AEs reported by Lot 4 subjects were judged to be definitely related to the vaccine. No AEs were graded by the Medical Reviewer as severe, nor were there any SAEs.

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8.2.5 Protocol 65-7: Evaluation of Attenuated Tularemia Vaccine (LVS) from National Drug [Biologic Research] Company

Among the 12 subjects in the study, 40 AEs were reported (39 local, 1 systemic), most of which were graded mild in severity (75%) by the Medical Reviewer and occurred in the first 7 days postvaccination (90%) with the exception of papule and maculopapule, which occurred between Days 8 and 14. All 12 subjects reported developing a small (less than 1 cm) erythematous maculopapular lesion at the vaccination site that resolved spontaneously. Maximum erythema (8 mm) was recorded for one subject on Day 7. The other most commonly reported AE was lymphadenopathy (9 subjects).

The majority (95%) of local reactions were judged to be definitely related to the vaccine. One case of fever and one case of pruritus were determined to be possibly related to the vaccine.

Table 15 shows the frequency of all AEs reported by body system and days postvaccination.

Table 15. Frequency of AEs Reported by Body System and Days Postvaccination

Event	Total Number of Subjects		Days Postvaccination			
	N = 12	%	1-3 days	4-7 days	8-14 days	≥15 days
Body as a Whole						
Fever	1	8	-	1	-	-
Cardiovascular						
None reported	-	-	-	-	-	-
Digestive						
None reported	-	-	-	-	-	-
Eyes, Ears, Nose, Throat						
None reported	-	-	-	-	-	-
Gastrointestinal						
None reported	-	-	-	-	-	-
Hemic and Lymphatic						
Lymphadenopathy	9	75	7	2	-	-
Metabolic & Nutritional Disorders						
None reported	-	-	-	-	-	-
Musculoskeletal						
None reported	-	-	-	-	-	-
Nervous System						
None reported	-	-	-	-	-	-
Respiratory						
None reported	-	-	-	-	-	-

N = Number of subjects

Table 16. Frequency of AEs Reported by Body System and Days Postvaccination (continued)

Event	Total Number of Subjects		Days Postvaccination			
	N = 12	%	1-3 days	4-7 days	8-14 days	≥15 days
Skin and Appendages						
Erythema	2	17	1	1	-	-
Induration	2	17	-	2	-	-
Macule	6	50	3	2	-	1
Maculopapule	8	67	7	-	1	-
Papule	11	92	1	8	2	-
Pruritus	1	8	-	1	-	-
Total AEs	40		19	17	3	1

N = Number of subjects

The rate of AEs was tabulated for each reaction and mean ages were computed for each AE (present or absent), but no discernible age trends were apparent. There were no SAEs reported nor were there any deaths. All AEs resolved without known sequelae. No subjects developed an actual or modified form of the natural disease, systemic allergic reaction, or GBS.

8.2.6 Protocol 65-4: Evaluation of Attenuated Tularemia Vaccine (LVS) from National Drug [Biologic Research] Company

A total of 33 AEs were reported among the 7 subjects during the study. All 7 of those subjects reported developing a small (less than 1 cm) erythematous maculopapular lesion, typically associated with vaccination, which resolved spontaneously. The most commonly reported AEs were lesions (7 subjects), papule (5 subjects), lymphadenopathy (5 subjects), pruritus (3 subjects), and vesicle (3 subjects). Table 16 shows the frequency of AEs reported, by body system and days postvaccination.

Table 17. Frequency of AEs Reported by Body System and Days Postvaccination

Event	Total Number of Subjects		Days Postvaccination			
	N = 7	%	1-3 days	4-7 days	8-14 days	≥15 days
Body as a Whole						
None reported	-	0	-	-	-	-
Cardiovascular						
None reported	-	0	-	-	-	-
Digestive						
None reported	-	0	-	-	-	-
Eyes, Ears, Nose, Throat						
None reported	-	0	-	-	-	-
Gastrointestinal						
None reported	-	0	-	-	-	-
Hemic and Lymphatic						
Lymphadenopathy	5	71.4	4	1	-	-
Metabolic & Nutritional Disorders						
None reported	-	0	-	-	-	-
Musculoskeletal						
None reported	-	0	-	-	-	-
Nervous System						
None reported	-	0	-	-	-	-
Respiratory						
None reported	-	0	-	-	-	-
Skin and Appendages						
Erythema	2	28.6	-	2	-	-
Lesion	7	100	7	-	-	-
Maculopapule	7	100	7	-	-	-
Papule	5	71.4	-	-	5	-
Pruritus	3	42.9	1	2	-	-
Pustule	1	14.3	-	-	1	-
Vesicle	3	42.9	-	3	-	-
Total AEs	33		19	8	6	0

N = Number of subjects

All AEs occurred within 7 days postvaccination with the exception of papule and pustule, which occurred between Days 8 and 14. AE rates were tabulated for each reaction, and mean age was computed for each AE (present or absent), but no discernible age trend was apparent. All AEs resolved without known sequelae. No subjects developed an actual or modified form of the natural disease, systemic allergic reaction, or GBS, which were possible, known risks of the vaccine. No deaths were reported during this study.

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The Medical Reviewer graded all AEs as mild. No reports of SAEs were reported. The Medical Reviewer also determined that the AEs reported were definitely (N = 30) or probably (N = 3) related to the vaccine.

8.2.7 Protocol AB-104: Evaluation of Stability and Protective Efficacy of Tularemia Vaccine, Live, Attenuated, among At-Risk Personnel

Several different lots of NDBR 101 tularemia vaccine were used in this study; however, only data from Lot 4 were extracted for this report as it is the lot being used in the current vaccination program. Of the 722 healthy subjects enrolled in the study, 720 received a primary vaccination and 2 received a booster shot. Six of the 722 subjects were given an additional vaccination of NDBR 101, Lot 4; however, the rationale for this is unknown. Of the 722 subjects enrolled, 720 completed the study (665 males, 55 females). Two subjects withdrew after vaccination for unknown reasons.

The term “booster” was assigned by data entry personnel only if the data sheet stated a booster was given, regardless of the number of vaccinations the subject may have received. Subjects were sometimes given an additional tularemia vaccination from a different lot if their titer levels were $<1:20$. Data entry personnel did not record this as a “booster” but rather as an additional vaccination.

Additionally, 6 subjects were given a skin test and some subjects were skin tested more than once; however again, the rationale for this is unknown.

The majority of participants were white (91%), male (92%), and between the ages of 20 and 29 (50%). Subjects participating in this study may have been simultaneously enrolled in other investigational protocols in which they received investigational or licensed products including anthrax, smallpox, yellow fever, and Q fever. Background medical conditions of subjects were recorded but not evaluated.

Recorded AEs were nonspecific, but historically were local (rather than systemic) reactions. During a retrospective review of the records, the medical reviewer determined the frequency, severity, and relationship of the AEs. Of the 720 subjects vaccinated with Lot 4 (not including those subjects who were boosted or who received a second vaccination), 43 subjects had no AEs data recorded. Of the remaining 677 subjects, 89 were classified as having experienced no AEs, leaving 588 subjects with one or more recorded AEs. A total of 532 subjects had AEs classified as “expected” nonspecific reactions, commonly known as a “take,” in which the reaction at the vaccination site progressed from a red papule to a vesicle to an eschar formation. There were just 90 AEs for which specific data were recorded.

Data on those 90 specific AEs primarily involved the skin and appendages (74 AEs) and hemic and lymphatic (7 AEs) body systems. AEs were also recorded for the body as a whole (6 AEs) and musculoskeletal body systems (3 AEs). Table 17 lists the 90 AEs that were recorded, by body system.

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Table 18. Frequency of AEs Reported by Body System

Event	N = 90
Body as a Whole	
Chills	1
Diaphoresis	1
Malaise	3
Swelling	1
Cardiovascular	-
None reported	
Digestive	-
None reported	
Eyes, Ears, Nose, Throat	-
None reported	
Gastrointestinal	-
None reported	
Hemic and Lymphatic	
Lymphadenopathy	7
Metabolic & Nutritional Disorders	-
None reported	
Musculoskeletal	
Joint pain	1
Myalgia	2
Nervous System	-
None reported	
Respiratory	-
None reported	
Skin and Appendages	
Blister	1
Erythema	4
Eschar	1
Induration	2
Lesion	50
Papule	6
Pruritus	8
Tenderness	1
Vesicle	1
Total AEs	90

N = Number of subjects

The majority of recorded AEs were either mild or moderate, or no data were available to make an assessment of severity. One AE was graded as severe (myalgia) and occurred within the first 3 days postvaccination and had no resolution data recorded. No SAEs were reported.

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8.3 TSI-GSD 213 Safety

8.3.1 Protocol 91-9, Log A-5588: Evaluation of the Safety and Immunogenicity of a Live Bacterial Tularemia Vaccine in Normal Adult Subjects

During the study, a total of 273 AEs were reported: 144 in the Lot 2R-85 cohort and 129 in the Lot 3-85 cohort (Table 18). The majority of AEs were reported within 7 days of vaccination (70.1% for subjects receiving Lot 2R-85 and 77.5% of subjects receiving Lot 3-85). Overall, more AEs were reported by those receiving vaccine from Lot 2R-85 than from Lot 3-85 (144 versus 129), but the difference was not considered to be statistically significant. Some reactions resolved after palliative treatment; all reactions resolved without sequelae.

Table 19. Frequency of AEs Reported by Study Lot

Event	Lot 2R-85 (Total = 144)				Lot 3-85 (Total = 129)			
	1-3 days	4-7 days	8-14 days	≥15 days	1-3 days	4-7 days	8-14 days	≥15 days
Body as a Whole								
Abdominal pain				1				
Chills						1		
Fatigue								1
Fever	1		1	2			1	
Headache	3	1	3	2	3	2	1	
Influenza								1
Malaise	1	2	2		2		1	
Pain				1		1		
Cardiovascular								
None reported								
Digestive								
Diarrhea				3		1		
Eyes, Ears, Nose, Throat								
None reported								
Gastrointestinal								
Elevated LFTs				1			1	
Emesis				1				
Gastrointestinal upset	1							1
Nausea				1	2			
Hemic and Lymphatic								
Lymphadenopathy	5	3	1	2	9	1	1	
Metabolic & Nutritional Disorders								
None reported								

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Table 18. Frequency of AEs Reported by Study Lot (continued)

Event	Lot 2R-85 (Total = 144)				Lot 3-85 (Total = 129)			
	1-3 days	4-7 days	8-14 days	≥15 days	1-3 days	4-7 days	8-14 days	≥15 days
Musculoskeletal								
Arthralgia		1			1			2
Back pain				1				
Myalgia	1	2	1	1	2		1	
Nervous System								
Dizziness					1			
Paresthesia							1	
Respiratory								
Congestion	1	1		2				
Cough				1				
Rhinorrhea	1			1			2	
Sore throat	2	1	1		1		1	
Skin and Appendages								
Lesion			1		1		1	3
Papule	39	5	3		38	5	1	
Pruritus	16	3			9	7		
Pustule	2	8	4	3	2	8	5	2
Pyuria					1			
Rash	1							1
Urogenital								
Vesicle			2	1		2	1	
Total	74	27	19	24	72	28	18	11

No difference between lots was detected in per-subject AE rates that were compared by Fisher's exact test, adjusted for multiple comparisons. Evidence of "take" was seen in all but 3 subjects. All 47 subjects (100%) receiving Lot 2R-85 experienced small (<1 x 1 cm) erythematous papular lesions typically associated with vaccination; whereas 44 of 47 subjects (93.6%) receiving Lot 3-85 reported this experience. All papular lesions resolved within 14 days without the administration of medication. Pustules developed in 17 of 47 subjects (36.2%) vaccinated with either Lot 2R-85 or Lot 3-85. All lesions healed by the completion of the study. These papular lesions were an expected occurrence of the vaccination and therefore considered to be related to the vaccine.

Mild adenopathy was observed in 11 of 47 (23.4%) of Lot 2R-85 and Lot 3-85 recipients. There were no significant differences in the date of onset, resolution, or frequency of adenopathy among subjects in either cohort.

In the Lot 2R-85 cohort, low-grade pruritus at the vaccination site and lymphadenopathy occurred in 19 (40.4%) and 11 (23.4%) subjects, respectively. Five subjects (10.6%) reported malaise, 9 subjects (19.1%) reported headache, 5 subjects (10.6%) reported

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myalgia, and 1 subject (2.1%) reported arthralgia. All reactions were considered either mild or moderate in nature.

In the Lot 3-85 cohort, low-grade pruritus at the vaccination site and lymphadenopathy occurred in 16 (34.0%) and 11 (23.4%) subjects, respectively. Three subjects (6.4%) reported malaise, 6 subjects (12.8%) reported headache, 3 subjects (6.4%) reported myalgia, and 3 subjects (6.4%) reported arthralgia. All reactions were considered either mild or moderate in nature.

Only one subject (a 34-year-old white male in the Lot 2R-85 group) reported a severe AE (mild fever, malaise, and myalgia along with a severe headache, all of which resolved within 9 days). The Medical Reviewer considered all the subject's complaints as "probably" related to the study vaccine.

No subjects developed an actual or modified form of the natural disease, systemic allergic reaction, or GBS.

8.3.2 Protocol 87-4, Log A-4706: Evaluation of New Lots of a Tularemia Vaccine, Protocol A: Initial Assessment of the Safety of *Francisella tularensis* Vaccine, Live, TSI-GSD 213, Lot 1R-85

A memo dated February 11, 1988, for the Deputy Commander for Development at USAMRIID brought the potential of liver complications to light. Therefore, as a safety precaution, subjects were vaccinated in groups of 4 (and later 10 to 12) until the maximum number of planned subjects was reached.

A total of 40 AEs were reported: 220 AEs in the vaccine group and 120 AEs in the placebo group (Table 19). All 34 subjects vaccinated with Lot 1R-85 and 32 of 35 placebo subjects reported at least 1 AE. Statistical findings for the adjusted p-value ($p < 0.05$) confirmed the differences in AE rates between vaccine and placebo treatment groups for injection site lesion (31 vaccine vs. 15 placebo), pruritus (17 vaccine vs. 4 placebo), induration (13 vaccine vs. 1 placebo), tenderness (10 vaccine vs. 0 placebo), and papule (9 vaccine vs. 0 placebo). Suggestive differences that met the unadjusted p-value were lymphadenopathy (11 vaccine vs. 3 placebo), erythema (17 vaccine vs. 7 placebo), macule (7 vaccine vs. 1 placebo), pustule (6 vaccine vs. 0 placebo), and vesicle (5 vaccine vs. 0 placebo).

Table 20. Frequency of AEs Reported for Each Treatment Group by Body System

Event	Vaccine (N = 34)		Placebo (N = 35)	
	Number of AEs	% of Subjects	Number of AEs	% of Subjects
Body as a Whole				
Abdominal distention	-	-	1	2.9
Anorexia	2	5.9	3	8.6
Chest pain	1	2.9	-	-
Chills	1	2.9	1	2.9
Elevated ALKP	-	-	1	2.9
Fatigue	2	5.9	-	-
Fever	3	8.8	2	5.7
Headache	13	38.2	17	48.6
Malaise	11	32.4	9	25.7
Pain	1	2.9	1	2.9
Cardiovascular				
None reported	-	-	-	-
Digestive				
None reported	-	-	-	-
Eyes, Ears, Nose, Throat				
Allergic rhinitis	2	5.9	1	2.9
Conjunctivitis	1	2.9	-	-
Otitis externa	1	2.9	-	-
Palpebral pruritus	-	-	1	2.9
Rhinorrhea	1	2.9	1	2.9
Sore throat	-	-	2	5.7
Toothache	1	2.9	-	-
Gastrointestinal				
Abdominal pain	4	11.8	6	17.1
Diarrhea	6	17.6	2	5.7
Elevated enzymes	-	-	1	2.9
Elevated LFTs	5	14.7	3	8.6
Emesis	-	-	2	5.7
GI upset	1	2.9	-	-
Hiccups	1	2.9	-	-
Nausea	2	5.9	8	22.9

N = Number of subjects

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Table 19. Frequency of AEs Reported for Each Treatment Group by Body System (continued)

Event	Vaccine (N = 34)		Placebo (N = 35)	
	Number of AEs	% of Subjects	Number of AEs	% of Subjects
Hemic and Lymphatic				
Abdominal node	-	-	1	2.9
Anemia	-	-	2	5.7
Congested vessels	1	2.9	-	-
Lymphadenopathy	11	32.4	3	8.6
Splenomegaly	1	2.9	1	2.9
Metabolic & Nutritional Disorders				
None reported	-	-	-	-
Musculoskeletal				
Arthralgia	1	2.9	1	2.9
Back pain	2	5.9	-	-
Joint pain	2	5.9	1	2.9
Knee pain	1	2.9	-	-
Myalgia	9	26.5	4	11.4
Nervous System				
Dizziness	4	11.8	1	2.9
Respiratory				
Congestion	1	2.9	2	5.7
Cough	3	8.8	5	14.3
URI symptoms	1	2.9	2	5.7
Skin and Appendages				
Cellulitis	-	-	1	2.9
Contact dermatitis	1	2.9	1	2.9
Contusion	-	-	1	2.9
Dermatitis	1	2.9	-	-
Dermatographia	-	-	1	2.9
Erythema	17	50.0	7	20.0
Induration	13	38.2	1	2.9
Keloid	1	2.9	-	-
Lesion (injection site)	31	91.2	15	42.9
Macule	7	20.6	1	2.9
Maculopapular rash	-	-	1	2.9
Nodule	-	-	1	2.9
Papule	9	26.5	-	-
Pruritus	17	50.0	4	11.4
Pustule	6	17.6	-	-

N = Number of subjects

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Table 19. Frequency of AEs Reported for Each Treatment Group by Body System (continued)

Event	Vaccine (N = 34)		Placebo (N = 35)	
	Number of AEs	% of Subjects	Number of AEs	% of Subjects
Skin and Appendages (cont'd.)				
Rash	3	8.8	1	2.9
Sterile abscess	1	2.9	-	-
Tenderness	10	29.4	-	-
Tinea cruris	1	2.9	-	-
Ulcer	1	2.9	-	-
Vesicle	5	14.7	-	-
Total AEs	220		120	

N = Number of subjects

Seven AEs were scored as severe, 4 from the vaccine group and 3 from the placebo group. The severe AEs in the vaccine group included lesion, injection-site sterile abscess, headache, and lymphadenopathy. The 3 severe AEs from the placebo group included headache (2 subjects) and abdominal pain (1 subject). During the postvaccination period, 7 subjects (3 vaccine vs. 4 placebo) had more than one episode of any single AE, including lesion, erythema, malaise, headache, nausea, diarrhea, lymphadenopathy, and myalgia. The most severe episode was used in the calculations.

Fifty-two percent (52%) of all AEs were reported within the first 3 days postvaccination. One subject was reported to have experienced an SAE, but it was later determined that the SAE was a manifestation of Hodgkin's disease and therefore not related to the administration of the vaccine.

Slightly more than half (116, [53%]) of the 220 AEs reported by subjects in the vaccine group were definitely related, 20 (9%) were probably related, 43 (20%) were possibly related, and 41 (19%) were either unrelated to the vaccine or there were no data recorded to form an association. Of the 120 AEs reported by the placebo group, 26 (22%) were related to the placebo, presumably from the vaccination procedure itself.

8.4 Aerosol Challenge Safety

8.4.1 Protocol 67-1: Respiratory *Pasteurella (Francisella) tularensis* in Man

A total of 45 PEs were reported, all for the 8 subjects in the virulent-challenge group who received between 18,480 and 30,156 virulent *F. tularensis* organisms. None of the placebo (nonvirulent challenge) controls reported PEs. The most common PEs in the virulent-challenge group were fever (8 subjects), headache (8 subjects), malaise (8 subjects), myalgia (7 subjects), and photophobia (6 subjects). Seven PEs were either mild or moderate in severity. Severe reactions (N = 9) included fever (5 subjects), headache

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(2 subjects), myalgia (1 subject), and photophobia (1 subject), all recorded within 7 days of aerosol exposure. All PEs, with the exception of rash, were judged by the Medical Reviewer to be definitely or probably related to the virulent challenge. No data were available to make a causal determination about the rash. All 8 virulent-challenge subjects reported fever (range mean 97.4°F to 103.1°F; maximum temperature [T_{max}] of 104°F recorded at Day 4). Table 20 lists the PEs reported by subjects in the virulent-challenge group.

Table 21. Frequency of AEs Reported by Virulent-Challenge Subjects by Body System

Event	Virulent-Challenge Group (N = 8)	
	Number of AEs	% of Subjects
Body as a Whole		
Chest pain	2	25.0
Fever	8	100.0
Headache	8	100.0
Malaise	8	100.0
Cardiovascular		
None reported		
Digestive		
None reported		
Eyes, Ears, Nose, Throat		
Photophobia	6	75.0
Gastrointestinal		
Nausea	3	37.5
Hemic and Lymphatic		
None reported	-	-
Metabolic & Nutritional Disorders		
None reported	-	-
Musculoskeletal		
Back pain	2	25.0
Myalgia	7	87.5
Nervous System		
None reported	-	-
Respiratory		
None reported	-	-
Skin and Appendages		
Rash	1	12.5
Total PEs	45	

N = Number of subjects

No SAEs were reported. The majority (31 of 45 or 68.9%) of PEs reported by all subjects had no data recorded to make a precise determination of severity.

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Most PEs were reported within the first 3 days (30 of 45 or 66.7%); the remaining PEs were reported between Days 4 and 7 postchallenge. All reactions are believed to have resolved without sequelae.

8.4.2 Protocol 65-13: Evaluation of Storage Stability of Living Vaccine Strain (LVS) of *Pasteurella tularensis* and Protocol 65-13A: Evaluation of Metabolic Changes in Immunized Subjects Exposed to Infectious Doses of *P. tularensis*

Protocol 65-13

A total of 14 subjects participated, 8 of whom were vaccinated by scarification (multiple puncture technique) in the right arm with either Lot 2 or Lot 4 of tularemia vaccine in Protocol 65-8. The remaining 6 subjects were unvaccinated controls. The level of protection afforded vaccinated and unvaccinated subjects against aerosol exposure of *F. tularensis* was assessed in this study by evaluating safety parameters of temperature, pulse, and PEs - defined as postchallenge AEs.

Vaccinated subjects who were exposed to a low-dose aerosol challenge of virulent SCHU-S4 *F. tularensis* organisms (range: 2,403 to 3,158) experienced fewer PEs and milder fever profiles than vaccinated subjects from the same study protocol who were exposed to a high-dose aerosol challenge with the same virulent organisms (range: 25,440 to 36,368). None of the low-dose challenge subjects who had been vaccinated with Lot 4 received antibiotic treatment; however, 1 low-dose challenge Lot 2 subject did receive streptomycin on Day 3 postchallenge. Streptomycin was also administered to all high-dose challenge subjects by Day 11 regardless of the vaccine lot they received in Protocol 65-8, as did all of the unvaccinated control subjects.

All 14 subjects reported a PE, the majority of which were from subjects in the high-dose challenge group having received Lot 4 and from unvaccinated control subjects. Fever, headache, and myalgia were the most frequently reported with fever and headache reported by all subjects and myalgia reported by 79% of subjects. A total of 76 PEs were reported, 62% of which occurred within 3 days postexposure. PEs included 15 severe, 16 moderate, and 27 mild. Of the 15 severe PEs recorded, all were resolved by Day 36. The remaining 18 PEs had no data from which to make a determination of severity. Table 21 illustrates the reported PEs by challenge group, lot, and body system.

Table 22. Frequency of AEs Reported by Challenge Group, Lot, and Body System

Event	Low-Dose Challenge			High-Dose Challenge			All N = 14
	Lot 2 N = 2	Lot 4 N = 2	Control N = 3	Lot 2 N = 1	Lot 4 N = 3	Control N = 3	
Body as a Whole	5	4	7	3	8	9	36
Anorexia					1		1
Chest pain	1			1		1	3
Disorientation					1	1	2
Elevated sedimentation rate			1				
Fever	2	2	3	1	3	3	14
Headache	2	2	3	1	3	3	14
Malaise						1	1
Cardiovascular	0	0	0	0	0	0	0
None reported	-	-	-	-	-	-	-
Digestive	0	0	0	0	0	0	0
None reported	-	-	-	-	-	-	-
Eyes, Ears, Nose, Throat	1	0	2	0	3	7	13
Conjunctival diffusion						1	1
Conjunctival injection	1		1		1	2	5
Coryza					1		1
Eyes burning						1	1
Ocular pain			1				1
Pharyngeal injection					1		1
Photophobia						1	1
Rhinorrhea						1	1
Sore throat						1	1
Gastrointestinal	0	1	1	0	1	0	3
Abdominal distention			1				1
Nausea		1			1		2
Hemic & Lymphatic	0	0	0	0	0	0	0
None reported	-	-	-	-	-	-	-
Metabolic & Nutritional Disorders	0	0	0	0	0	0	0
None reported	-	-	-	-	-	-	-
Musculoskeletal	1	1	3	1	4	3	13
Back pain			1		1		2
Myalgia	1	1	2	1	3	3	11

N = Number of subjects

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Table 21. Frequency of AEs Reported by Challenge Group, Lot, and Body System (continued)

Event	Low-Dose Challenge			High-Dose Challenge			All N = 14
	Lot 2 N = 2	Lot 4 N = 2	Control N = 3	Lot 2 N = 1	Lot 4 N = 3	Control N = 3	
Nervous System	0	0	0	0	2	1	3
Dizziness						1	1
Lethargic					1		1
Numbness					1		1
Respiratory	0	0	3	0	2	0	5
Chest infiltrates			1				1
Cough			1		1		2
Rales			1				1
URI symptoms					1		1
Skin and Appendages	1	0	1	0	0	1	3
Folliculitis	1						1
Rash			1			1	2
Total PEs	8	6	17	4	20	21	76

N = Number of subjects

The Medical Reviewer determined that approximately 80% of the severe PEs reported were probably related to the aerosol challenge. Most severe PEs required medication and all resolved without known sequelae.

Protocol 65-13A

All 8 subjects reported a PE, the majority of which were from subjects in the high-dose challenge group who had received vaccine from Lot 2. Fever, headache, and conjunctival injection were the most frequently reported of the 37 PEs with fever and headache reported by 6 of the 8 subjects and conjunctival injection reported by 5 of the 8 subjects. Well over half of the reported PEs (65%) occurred within 3 days postexposure. Table 22 lists the reported PEs by challenge group, lot, and body system.

Table 23. Frequency of AEs Reported by Challenge Group, Lot, and Body System

Event	Low-Dose Challenge		High-Dose Challenge		All N = 8
	Lot 2 N = 2	Lot 4 N = 2	Lot 2 N = 3	Lot 4 N = 1	
Body as a Whole	3	4	10	3	20
Facial flushing		2	1	1	4
Fever	1	1	3	1	6
Headache	1	1	3	1	6
Lethargic			1		1
Malaise	1		2		3

N = Number of subjects

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Table 22. Frequency of AEs Reported by Challenge Group, Lot, and Body System
(continued)

Event	Low-Dose Challenge		High-Dose Challenge		All N = 8
	Lot 2 N = 2	Lot 4 N = 2	Lot 2 N = 3	Lot 4 N = 1	
Cardiovascular	0	0	0	0	0
None reported	-	-	-	-	-
Digestive	0	0	0	0	0
None reported	-	-	-	-	-
Eyes, Ears, Nose, Throat	4	2	4	2	12
Aphthous ulcers	1				1
Conjunctival injection	1	1	2	1	5
Coryza			1	1	2
Rhinorrhea			1		1
Sore throat	1	1			2
Tinnitus	1				1
Gastrointestinal	0	0	1	0	1
Diarrhea			1		1
Hemic & Lymphatic	0	0	0	0	0
None reported	-	-	-	-	-
Metabolic & Nutritional Disorders	0	0	0	0	0
None reported	-	-	-	-	-
Musculoskeletal	0	0	2	1	3
Myalgia			2	1	3
Nervous System	0	0	0	0	0
None reported	-	-	-	-	-
Respiratory	0	0	1	0	1
Pneumonitis			1		1
Skin and Appendages	0	0	0	0	0
None reported	-	-	-	-	-
Total PEs	7	6	18	6	37

N = Number of subjects

The Medical Reviewer graded all PEs (for which there were data) as mild, moderate, or severe. The 37 recorded PEs included 15 mild, 4 moderate, and 4 severe. Thirteen PEs had no severity data recorded. Six of 8 subjects reported fever and headache, 5 subjects reported conjunctival injection, and 4 subjects reported facial flushing. Of the 4 severe PEs recorded, all were resolved by Day 9; however, data were not available on 1 subject. Nearly 76% of the PEs reported were judged by the Medical Reviewer to be definitely related to the aerosol challenge; the remaining PEs were judged to be probably related (11%), possibly related (5%), or unrelated (5%) to the aerosol challenge. There was 1 subject for whom no data were recorded (3%).

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8.5 Skin Test Antigen Safety

8.5.1 Protocol 75-2: Evaluation in Volunteers of the A-RFC Test as an Assay for Previous Immunization to Tularemia

A positive skin test was defined as a subject with induration of ≥ 0.5 cm at the skin test site at 48 hours. Of the skin-test-positive persons, 75% had induration or edema measuring 0.7 to 3 cm in diameter at the skin test site; a smaller percentage had reactions extending from 3 to 12 cm. No subject had local reactions consisting of axillary node tenderness or limitation of arm movement because of pain or swelling. No one developed a cyst, abscess, necrosis, or dermal slough at the skin test site. In summary, the tularemia skin test reactions produced by the skin test vaccine lot used in this study seemed to be no more frequent and perhaps less severe than those observed after administration of intermediate-strength tuberculin skin (tine) test between 1956 and 1970.

No AEs or deaths were reported during the study period. No adverse local or systemic reactions to the skin test antigen were noted in the clinical presentation or in the white blood cell (WBC) counts of 9 subjects examined daily for 7 days.

8.6 Serious Adverse Events

Two SAEs, defined as resulting in death, a life-threatening AE, an inpatient hospitalization, a persistent or significant disability/incapacitation, or a congenital anomaly/birth defect, were documented, one in Protocol 87-4 and the other in Protocol 87-9. The subject in Protocol 87-4 was hospitalized with fever and diffuse adenopathy but was later diagnosed with Hodgkin's disease, nodular sclerosing variety, that was most likely present prior to the subject's enrollment in the study. It, therefore, was determined that this SAE was unrelated to the administration of the vaccine. No safety reports were required to be submitted to FDA.

The subject in Protocol 87-9 was seen as an outpatient in the emergency room complaining of eye pain and loss of vision. The subject had been vaccinated 4 years prior to the AE, was enrolled in multiple protocols, and was also predisposed to HLA-B27-associated uveitis because of an autoimmune condition. The causal relationship of the SAE reported for the Protocol 87-9 subject was thoroughly reviewed and was conclusively determined unlikely to be related to the administration of the vaccine.

No subject developed an actual or modified form of the natural disease, and no systemic allergic reactions or GBS were attributed to the live, attenuated tularemia vaccine(s) used in these studies.

8.7 Deaths

No deaths were reported.

8.8 Withdrawal from Study due to Adverse Events

No withdrawals due to the occurrence of AEs were reported in any of the studies.

9 Clinical Laboratory Data

The profile of clinical laboratory data is provided in this section. It should be noted that data were not uniformly collected in every study and due to the age of some of the studies, reference ranges from the 87-4 study were used as surrogate reference points.

9.1 Summary of Elevated Transaminase Findings

LFT data were collected in only four of the studies. None of the 20 subjects vaccinated with Lot 4 (Part I of Protocol 68-4) had an LFT out of the established reference range and only 2 subjects (10%), both noncontrols in the high-dose challenge group, had an ALT and AST value outside the established reference range. Data available on 121 subjects vaccinated with NDBR 101, Lot 11 (Protocol 87-9) showed 22 subjects (18.2%) had an elevated ALT value and 16 subjects (13.2%) had an elevated AST level. Most of the elevated readings were short-lived as elevated ALT values for 14 of the 22 subjects (64%) and elevated AST values for 13 of the 16 subjects (81%) returned to within normal limits at Day 1.

In the TSI-GSD 213 studies, data were not available on all 47 subjects in each treatment group; however, elevated ALT levels were seen in 5 of 42 subjects (10.6%) vaccinated with Lot 2R-85 and in 2 of 45 subjects (4.3%) vaccinated with Lot 3-85 (Protocol 91-9). Elevated AST levels were reported in 5 of 42 subjects (10.6%) vaccinated with Lot 2R-85 and 1 of 46 subjects (1.6%) vaccinated with Lot 3-85. In Protocol 87-4, elevated ALT levels were seen in 9 of 34 subjects (26.5%) vaccinated with TSI-GSD 213, Lot 1R-85 and in 6 of 35 subjects (17.1%) given placebo. Elevated AST levels were also seen in 12 of 34 subjects (35.3%) vaccinated with Lot 1R-85 and in 11 of 35 subjects (31.4%) given placebo.

It is important to note that elevations in the transaminase levels were almost always explainable (i.e., pre-existing or known etiology) and/or returned to within normal limits without sequelae. Table 23 lists the number of subjects with an LFT value above the established reference range for the four studies in which data were collected.

Table 24. Abnormal Liver Function Test Values (Above Normal Limits) at Any Time Point for Primary and Booster Vaccinations

Laboratory Test and Range Normal	NDBR 101				TSI-GSD 213							
	Protocol 87-9		Protocol 68-4/ Protocol 68-4A		Protocol 91-9				Protocol 87-4			
	Lot 11		Lot 4		Lot 2R-85		Lot 3-85		Lot 1R-85		Placebo	
	N	%	N	%	N	%	N	%	N	%	N	%
ALT (0 - 50 IU/L)	22	18.2	0	n/a	5	10.6	2	4.3	9	26.5	6	17.1
AST ¹ (10 - 42 IU/L)	16	13.2	0	n/a	5	10.6	1	2.1	12	35.3	11	31.4

N = Number of subjects

¹ AST reference range in Protocol 91-9 was 0 - 50 IU/L.

9.1.1 Protocol 87-9 (NDBR 101, Lot 11)

Of 284 subjects, LFT data were available on only 117. Out-of-reference range rates for selected laboratory tests were analyzed by Fisher's exact test, adjusted for multiple comparisons. Elevated transaminase levels were of doubtful clinical significance as the majority were either pre-existing or had an explanation that included documented etiology. The Medical Reviewer noted that the majority of subjects had elevated LFTs prior to vaccination, some for years. There were 30 subjects (29 males, 1 female) with elevated LFT levels (ALT or AST) after vaccination, 28 of whom had documented etiology that included hepatitis B virus (HBV), hepatitis C virus (HCV), obstructed gall bladder, diet restrictions, and alcohol use. Documented etiology for these subjects along with a written narrative is available in Appendix 14.1.

9.1.2 Protocol 68-4/68-4A (NDBR 101, Lot 4)

LFTs (ALT, AST) were available from 16 of the 20 study subjects at Day 56. ALT and AST levels for all 16 subjects were within the reference range (ALT 0 - 50 IU/L; AST 10 - 42 IU/L) used in the analysis. In the second part of the study, LFTs (ALT and AST) were available from all 20 subjects following aerosol challenge. Subjects with elevated ALT or AST levels postchallenge (Day 0 or greater) occurred in only 2 subjects, both of whom were noncontrols in Group 2 (high-dose aerosol challenge). There were no out-of-reference range LFT levels at baseline.

9.1.3 Protocol 91-9 (TSI-GSD 213, Lots 2R-85 and 3-85)

Five of 42 subjects (10.6%) receiving Lot 2R-85 and 2 of 45 subjects (4.3%) receiving Lot 3-85 demonstrated elevated ALT (reference range 0 - 50 IU/L, $p=0.43$). Likewise, 5 of 42 subjects (10.6%) receiving Lot 2R-85 and 1 of 46 subjects (2.1%) receiving Lot 3-85 demonstrated elevated AST (reference range 10 - 50 IU/L, $p=0.20$). With the exception of 1 subject (who was positive for hepatitis C), all transaminase elevations were transient and/or of doubtful clinical significance. Nonetheless, transaminase elevations occurred more frequently postvaccination in Lot 2R-85 subjects than Lot 3-85 subjects, although not at elevated levels that were statistically significant. It should also be noted that the subjects in this study were members of the general population who were not at risk of tularemia infection. These subjects were paid for their participation and many were homeless as evidenced by the documented difficulty in trying to locate them for follow up study visits.

There were no differences between lots in the rates of elevated ALT ($p=0.435$) or AST ($p=0.204$). The majority of ALT and AST elevations were transient although some were pronounced and of longer duration lasting more than 41 weeks (291 days). Documented etiology for these subjects along with a written narrative is available in Appendix 14.2.

9.1.4 Protocol 87-4 (TSI-GSD 213, Lot 1R-85)

AST and ALT levels were recorded for subjects enrolled in vaccine (N = 34) and placebo (N = 35) treatment groups. Fisher's exact test (2-tailed) was used to compare the rates of elevated out-of-reference-range LFTs postvaccination to include the possibility of either an increase or decrease in the rates in the vaccine group relative to the placebo group. P-values were 0.39 and 0.80 for ALT and AST, respectively, and 0.81 for subjects with either elevated AST or ALT (or both). There was no statistical evidence of a difference in elevated out-of-reference-range LFT rates between treatment groups at the 95% CI. In the vaccine group, there were 14 (41%) subjects with elevated LFTs of which 5 were related to alcohol use, 3 were elevated prior to vaccination, and 6 were of unknown etiology. There were 13 (37%) subjects in the placebo group with elevated LFTs of which 5 were related to alcohol use and 8 were of unknown etiology. Table 26 lists the documented etiology for 9 subjects with elevated LFTs (ALT and/or AST). Documented etiology for these subjects along with a written narrative is available in Appendix 14.3.

9.2 NDBR 101 Studies Laboratory Data

9.2.1 Protocol 99-2, Log A-8573: A Longitudinal Phase 2 Multi-Site Study for the Continued Evaluation of the Safety and Immunogenicity of a Live *Francisella tularensis* Vaccine, NDBR 101

All laboratory findings for the one subject who was vaccinated with NDBR 101, Lot 11, with the exception of cholesterol and low density lipoproteins (LDL), were within normal limits. Biological reactions and vital signs including temperature, blood pressure, and pulse were unremarkable.

9.2.2 Protocol 87-9, Log A-4707: Evaluation of New Lots of Tularemia Vaccine, Protocol B: Comparative Assessment of *Francisella tularensis* Vaccine, Live, TSI-GSD 213 Lot 1R, and *Francisella tularensis* Vaccine, Live, NDBR 101 Lot 11

Postvaccination clinical laboratory values for the majority of the 284 subjects were within normal limits. Laboratory values outside (either above or below) normal limits returned to normal and without sequelae by Day 261 for all subjects. The number and percentage of subjects with outlying laboratory values at any time point in the study are presented in Table 24.

Table 25. Abnormal Laboratory Values at Any Time Point for Primary and Booster Vaccinations

Laboratory Test and Range Normal	Above Normal Limits		Resolution by Day	Below Normal Limits		Resolution by Day
	N	%		N	%	
HCT (males 39.5 - 50.4%) (females 34.6 - 45.7%)	2	1.7	1	3	2.5	26 ^a
Creatinine 0.6 - 1.4 mg/dL	1	0.8	1	-	-	-
HGB (males 13.2 - 17 g/dL) (females 11.6 - 15.1 g/dL)	4	3.3	1	1	0.8	26
PLT 150 - 466 x 10 ³ /mm ³	1	0.9	1	2	1.7	1
WBC 3.2 - 10.8 x 10 ³ /mm ³	6	5.0	14 ^b	-	-	-

N = Number of subjects

HCT = Hematocrit

PLT = Platelet Counts

HGB = Hemoglobin

WBC = Leukocyte Count

a 2 of 3 subjects (67%) resolved at Day 1.

b 5 of 6 subjects (83%) resolved at Day 1.

Hematocrit and Hemoglobin

Three of 120 subjects with laboratory values recorded showed a mild drop in HCT postvaccination and 1 subject exhibited a mild decline in HGB measurement postvaccination. Of 120 subjects with documented lab values, 2 and 4 showed increases in HCT and HGB, respectively.

Platelet Counts

Subject 739 was the only subject with a modest elevation of platelets (467 x 10³/mm³, reference range: 150-466 x 10³/mm³) of those with documented laboratory values. This was not considered clinically significant. Only 2 subjects (764 and 956) met the definition of postvaccination thrombocytopenia (<150 x 10³/mm³), both with a value of 133 x 10³/mm³.

Leukocyte Count

Eight subjects (1880, 1180, 235, 430, 463, 720, 951, and 962) had at least one elevated leukocyte (WBC) value (>10.8 x 10³/mm³) after vaccination. The maximum WBC value was 17.8 x 10³/mm³ documented prevaccination at Day -21 (Subject 1880); otherwise, the maximum value was documented at Day 7 (Subject 1180; 16.7 x 10³/mm³).

Leukopenia (<3.2 x 10³ leukocytes/mm³) was not observed in any of the subjects postvaccination.

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Urinalysis

Evaluation of urine specific gravity, pH, bilirubin, blood, glucose, and ketones produced unremarkable findings.

Biological Reaction and Vital Signs

Systolic and diastolic blood pressure (mmHg), erythema (mm), induration (mm), pulse (bpm), and temperature (°F) were among the vital signs measured and recorded postvaccination. It should be noted that data were not collected uniformly across subjects.

Systolic Blood Pressure and Diastolic Blood Pressure, Pooled by Location

Data showed mean blood pressure measurements to be within normal limits in subjects at all study locations. Blood pressure was tested by a mixed model analysis of variance (ANOVA) for location effects and time trends over Days 1, 2, and 7. None were detected.

Erythema and Induration

Data showed decreasing time trends for maximum erythema and maximum induration measurements, indicating resolution of local reactions during this period.

Pulse and Temperature

Pulse and temperature were tested by a mixed model ANOVA for location effects and time trends over Days 1, 2, and 7. No notable changes in mean pulse or temperature were detected.

9.2.3 Protocol 68-4 and 68-4A: Evaluation of Storage Stability of Tularemia Vaccine, Live, Attenuated NDBR 101, Lot 4**Clinical Safety (Part I)**

Again, reference ranges for laboratory results from 1967 were not available so surrogates from a subsequent study (Protocol 87-4) were used. Laboratory tests conducted were not protocol-specific (the database was shared among multiple Special Immunizations Program [SIP] investigational protocols); hence, only selected tests were analyzed.

Pharyngeal Washing and Throat Culture Studies

Pharyngeal culture assays were obtained on Day 57 and served as a baseline for Part II of the study. Results show 6 subjects with *F. tularensis* growth and 10 subjects with no *F. tularensis* growth at baseline.

Biological Reactions and Vital Signs

Temperature (°F), erythema (mm), and induration (mm) were among the vital signs measured and recorded on study visits at Days 0, 1, 3, 8, 14, 21, and 28.

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Temperature

T_{max} recorded was 98.8°F on Day 0 (SD ± 0.83) and on Day 14 (SD ± 0.92). No subjects experienced a fever, defined as ≥100°F.

Erythema and Induration

Out of 20 subjects, the mean erythema measured at Day 3 was 7.3 mm (SD ± 3.85); maximum measured erythema of 80 mm was recorded on Day 8 (SD ± 19.52). Out of 15 subjects, the mean induration measured at Day 3 was 5.3 mm (SD ± 2.49); maximum measured induration of 10 mm (SD ± 2.78) was recorded also on Day 3. Maximum local erythema and induration measurements were recorded on study visits at Days 0, 1, 3, 8, 14, 21, and 28.

Clinical Safety (Part II)

Again, since reference ranges for laboratory results from 1967 were not available, surrogates from a subsequent study (Protocol 87-4) were used. Laboratory tests conducted were not protocol-specific (the database was shared among multiple SIP investigational protocols); hence, only selected tests were analyzed.

Pharyngeal Washing and Throat Culture Studies

Pharyngeal washes and throat cultures were taken from Day -1 to Day 15 postchallenge, with the exception of Subject 9068 whose throat cultures were repeated to Day 26 due to positive growth. Cultures and washes were to be taken twice per day (morning and evening), but this could not be verified in all subjects; therefore, only morning results are reported. Positive *F. tularensis* growth in pharyngeal washes was observed at Day -1 in 7 of 20 subjects including 1 control subject from the low-dose group (Subject 9090). By Day 2 postchallenge, 4 subjects from Group 1 and 7 subjects from Group 2 had detectable growth. By Day 15 these rates dropped to 3 (Group 1) and 3 (Group 2). Table 25 illustrates the results throughout the study.

Table 26. Pharyngeal Wash Assays

Low-Challenge Group Subject Number	Study Day																
	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
9062	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
9063	-	-	+	+	+	+	+	+	+	-	-	-	-	-	-	-	+
9064	-	-	-	-	+	-	-	-	+	-	-	+	-	+	-	-	- ¹
9087	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-	-	- ²
9091	+	+	-	+	+	+	+	-	-	-	-	+	-	-	-	-	- ³
9092	-	-	+	-	-	-	-	-	-	+	-	-	-	+	-	-	-
9095	+	+	-	+	+	+	+	-	+	-	+	+	-	+	+	-	+
9096	-	-	+	-	-	-	-	-	-	-	-	-	+	-	-	-	+
9086 (control) ⁴	-	-	+	-	-	+	-	+	-	-	-	-	-	-	-	-	-
9090 (control) ⁴	+	+	+	+	+	+	+	+	+	-	-	-	+	-	-	-	-
High-Challenge Group Subject Number	Study Day																
	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
9065	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	-
9066	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	+
9068 ⁵	-	-	-	+	-	+	+	+	-	+	+	+	+	+	+	+	+
9071	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
9072	-	-	+	+	-	-	-	-	-	-	-	-	+	+	-	-	-
9084	+	+	+	+	+	+	+	+	+	-	+	-	+	-	-	+	-
9085	+	+	+	+	+	+	+	-	+	+	+	-	+	-	-	-	-
9094	-	-	+	+	+	+	+	+	+	-	-	-	-	+	+	-	-
9067 (control) ⁴	-	-	-	-	-	+	+	-	-	-	-	-	+	-	+	-	+
9089 (control) ⁴	-	-	-	-	-	-	-	-	+	-	-	-	+	-	-	-	-

Day -1 relative to challenge (Part II) equals Day 57 relative to vaccination (Part I)

+ Growth

- No growth

¹ U55-98-6835: Day 15, gram negative on all plates

² U56-42-0954: Day 15, all plates large gram negative rods

³ U55-88-2268: Day 15, overgrown with gram negative rods

⁴ Streptomycin initiated (1 g IM, BID, 7 days) to controls by Day 8.

⁵ Assays were continued to Day 26; streptomycin initiated at Day 22 for this subject. Growth continued to appear until Day 23. Subject was negative for growth Days 24 through 26.

Results from the sputum revealed *F. tularensis* growth on one plated sample from Day 15 through Day 26.

Vital Signs

Temperature (°F), pulse (bpm), and blood pressure (mmHg) were among the vital signs measured and recorded daily from Day 0 to Day 15. $T_{\max}$ postchallenge ranged from 101.6°F to 103.8°F in control subjects (Group 1 or Group 2); 100°F to 101°F in Group 1 subjects, and 99.6°F to 103°F in Group 2. All but one subject (Subject 9085 from Group 2) experienced a fever, defined as $\geq 100^\circ\text{F}$.

A comparison of the trends of mean vitals in the vaccinated subjects using a mixed model ANOVA indicated temperature means that were different between Group 1 and Group 2 ($p < 0.0001$). Compared with subjects in Group 1, subjects in Group 2 experienced mean

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temperature elevations at Days 3 and 4 postchallenge. Temperatures continued to be elevated for some subjects to Day 11.

Pulse and blood pressure measurements for all subjects were within acceptable limits. No statistical differences in trends between challenged subjects in Group 1 and Group 2 were detected for pulse or blood pressure.

9.2.4 Protocol 65-8: Evaluation of Attenuated Tularemia Vaccine (LVS) from National Drug [Biologic Research] Company

Again, reference ranges for laboratory results from 1964 and 1965 were not available so surrogates from a subsequent study (Protocol 87-4) were used; however, only selected tests were analyzed.

Laboratory data are available only on 5 Lot 2 subjects and 8 Lot 4 subjects. Four subjects had elevated HCT levels (1 Lot 2 subject; 3 Lot 4 subjects); 3 subjects had low HGB levels (all Lot 4 subjects); and 3 subjects had a high sedimentation rate (all Lot 4 subjects). All out-of-reference-range measurements were observed 85 days postvaccination or greater. Due to differential data loss between the lots, statistical comparison could not be computed.

Biological Reactions and Vital Signs

Erythema (mm) and induration (mm) were not routinely measured; temperature (°F) was not measured at all. There are only two measurements of erythema in the data, the maximum reading being 5.0 mm.

Pharyngeal Washes and Throat Cultures

Pharyngeal washes and throat cultures were not listed in the study procedures; however, the procedures were necessary for the 8 subjects who would participate in the 65-13A companion study.

9.2.5 Protocol 65-7: Evaluation of Attenuated Tularemia Vaccine (LVS) from National Drug [Biologic Research] Company

The protocol did not include laboratory tests as a study procedure. Local reactions and erythema/induration measurements for only 4 subjects were recorded. Maximum erythema was recorded for Subject 808 on Day 7 (8 mm) and for Subject 9075 on Day 1 (2 mm). Maximum erythema/induration was recorded for Subject 9074 on Day 21 and maximum induration for Subject 9081 was recorded on Day 5.

9.2.6 Protocol 65-4: Evaluation of Attenuated Tularemia Vaccine (LVS) from National Drug [Biologic Research] Company

The protocol did not include laboratory tests or vital signs as a study procedure. Only one erythema measurement was documented within the participant's study records. Subject 9103 had an erythema measurement of 2 mm.

9.2.7 Protocol AB-104: Evaluation of Stability and Protective Efficacy of Tularemia Vaccine, Live, Attenuated, among At-Risk Personnel

Again, reference ranges for laboratory results from 1965 were not available so surrogates from a subsequent study (Protocol 87-4) were used. Laboratory tests conducted were not protocol-specific (the database was shared among multiple SIP investigational protocols); hence, only selected tests were analyzed.

Pharyngeal Washing and Throat Culture Studies

Pharyngeal washes were not a study procedure listed in the study protocol but may have been done as a precaution if the subject had complained of a sore throat. A positive pharyngeal culture assay was observed on Day 13 from Subject 9215; however, the growth was negative for tularemia.

Throat culture assays were also not a study procedure listed in the study protocol; however, data were recorded for 21 subjects at multiple time points, none of whom were positive for tularemia.

Biological Reactions and Vital Signs

Reported local reactions, including erythema (mm), were restricted to within 28 days of vaccination and/or up to 1 year postvaccination.

Induration (mm) measurements are also listed up to 1 year postvaccination. Measurements of temperature or blood pressure were not recorded in this study.

9.3 TSI-GSD 213 Studies Laboratory Data

9.3.1 Protocol 91-9, Log A-5588: Evaluation of the Safety and Immunogenicity of a Live Bacterial Tularemia Vaccine in Normal Adult Subjects

Postvaccination clinical laboratory values for the majority of subjects were within normal limits. Subjects whose laboratory values were outside normal limits returned to normal and without sequelae by Day 291. (One subject continued to be followed clinically after study conclusion.) Creatinine and total bilirubin values were within normal limits at all time points for all subjects. The number and percentage of subjects with outlying laboratory values at any time point in the study are presented in Table 26.

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Table 27. Abnormal Laboratory Values at Any Time Point

Laboratory Test and Range Normal	Lot 2R-85				Lot 3-85			
	Above Normal Limits		Below Normal Limits		Above Normal Limits		Below Normal Limits	
	N = 47	%	N = 47	%	N = 47	%	N = 47	%
HCT (males 39 - 55%) (females 36 - 48%)	1	2.1	15	31.9	0	0	9	19.1
HGB (males 13.9 - 18 g/dL) (females 12 - 16 g/dL)	1	2.1	16	34.0	0	0	12	25.5
PLT 140 - 440 x 10 ³ /mm ³	7	14.9	2	4.3	0	0	0	0
WBC 4 - 10.5 x 10 ³ /mm ³	6	12.8	6	12.8	4	8.5	9	19.1

N = Number of subjects

HCT = Hematocrit

PLT = Platelet Counts

HGB = Hemoglobin

WBC = Leukocyte Count

Hematocrit and Hemoglobin

Fifteen of 47 (31.9%) subjects vaccinated with Lot 2R-85 and 9 of 47 (19.1%) subjects vaccinated with Lot 3-85 showed a mild drop in HCT postvaccination ($p=0.24$). Likewise, 16 of 47 (34.0%) subjects vaccinated with Lot 2R-85 and 12 of 47 (25.5%) subjects vaccinated with Lot 3-85 exhibited a mild decline in HGB measurement postvaccination ($p=0.50$). Some of these subjects had similarly low baseline measurements. Subject 10294 in the 2R-85 group also showed a mild HGB and HCT elevation, but further evaluation revealed that baseline readings and subsequent measurements were within the same elevated range.

There was no evidence that the frequency of elevated or decreased HGB and HCT readings were different between volunteers in the Lot 2R-85 cohort or the Lot 3-85 cohort.

Platelet Counts

Thrombocytosis (platelets $>440 \times 10^3/\text{mm}^3$) was observed in 7 of 47 (14.9%) Lot 2R-85 recipients postvaccination, but 0 of 47 (0%) Lot 3-85 recipients had elevations ($p=0.01$). These 7 subjects had modest elevations of platelets ($446-572 \times 10^3/\text{mm}^3$). None of the observed values were considered clinically significant. All were transient, three lasting 1 day only, one lasting 1 week, and three lasting 2 weeks.

Two subjects in the Lot 2R-85 cohort met the definition of postvaccination thrombocytopenia ($<140 \times 10^3/\text{mm}^3$) versus 0 of 47 subjects in the Lot 3-85 group ($p=0.49$). Subject 9862 (22-year-old white male) had a low platelet count on Day -7 of $139 \times 10^3/\text{mm}^3$. By Day 1 of the study, the subject's platelet count had decreased to $115 \times 10^3/\text{mm}^3$, which returned to normal by Day 2. Subject 10185 (39-year-old black

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male) had a low platelet count on Day 1 of $112 \times 10^3/\text{mm}^3$, which returned to normal by Day 7. None of these values represent clinically significant thrombocytopenia.

Leukocyte Count (WBC)

Among the 47 recipients of Lot 2R-85, 6 subjects (12.8%) had at least one elevated WBC value ($>10.5 \times 10^3/\text{mm}^3$) after inoculation, whereas 4 of the 47 subjects (8.5%) receiving Lot 3-85 had at least one elevated WBC recorded ($p=0.74$). The maximum WBC value observed was $14,000/\text{mm}^3$. Leukopenia ($<4.0 \times 10^3$ leukocytes/ mm^3) was observed at least once postvaccination in 6 of 47 (12.8%) Lot 2R-85 recipients and in 9 of 47 (19.1%) Lot 3-85 recipients ($p=0.57$). Leukopenia was neither progressive nor regarded as clinically significant in any subject. The minimum WBC observed was $2,700/\text{mm}^3$ on 1 day in a subject whose baseline was $3,900/\text{mm}^3$.

Urinalysis

There was no clear temporal pattern of urinary abnormalities. A total of 25 subjects had one or more abnormal findings. In all but 4, resolution of these abnormalities was documented (usually by follow-up specimens after completion of the menstrual period and/or carefully supervised clean-catch procedure). Subject 10187 had persistent leukocyte esterase (and microscopic pyuria) on three specimens. This was asymptomatic and cleared spontaneously, and urine culture was negative on two subsequent occasions.

Biological Reaction and Vital Signs

Systolic and diastolic blood pressure (BPS and BPD) (mmHg), erythema (mm), induration (mm), pulse (bpm), and temperature ($^{\circ}\text{F}$) were among the vital signs measured and recorded on Days 0, 1, 2, 4, 7, 14, and 21.

Systolic Blood Pressure and Diastolic Blood Pressure

Data showed mean blood pressure measurements to be within normal limits in subjects in both cohorts. BPS and BPD measurements for subjects in the two cohorts were comparable (Table 27).

Table 28. Mean Blood Pressure Readings

Evaluation Day	Lot 2R-85			Lot 3-85		
	N	Mean Systolic (mmHg)	Mean Diastolic (mmHg)	N	Mean Systolic (mmHg)	Mean Diastolic (mmHg)
0	41	118.2	73.7	43	119.4	75.5
1	47	115.9	73.8	47	117.6	74.5
2	46	116.7	72.5	47	118.0	73.6
4	46	116.0	73.6	45	117.4	74.0
7	47	115.4	74.1	47	117.4	75.0
14	46	116.0	71.9	47	117.4	73.1
21	20	114.0	72.7	22	117.0	74.4

N = Number of subjects

Both BPS and BPD measurements were slightly higher in subjects receiving Lot 3-85 than in Lot 2R-85.

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Erythema and Induration

Based on measurement values of erythema and induration, there was a difference in maximum dimension of erythema ($p=0.0011$), with subjects in the Lot 3-85 cohort having slightly higher mean values over time than subjects in the Lot 2R-85 cohort. This may be due to the 2 additional female subjects in the Lot 3-85 group compared with the Lot 2R-85 group and the tendency of females to exhibit greater erythema values. Maximum erythema and induration measurements are shown in Table 28.

Table 29. Maximum Erythema and Induration Measurements

Evaluation Day	Maximum Erythema (mm)				Maximum Induration (mm)			
	Lot 2R-85		Lot 3-85		Lot 2R-85		Lot 3-85	
	N	Mean $\pm$ SD	N	Mean $\pm$ SD	N	Mean $\pm$ SD	N	Mean $\pm$ SD
0	0	-	0	-	0	-	0	-
1	43	7.8 $\pm$ 2.27	47	9.9 $\pm$ 3.84	21	6.5 $\pm$ 1.83	28	10.0 $\pm$ 4.50
2	46	8.3 $\pm$ 2.65	47	11.7 $\pm$ 4.99	26	6.7 $\pm$ 1.91	34	9.6 $\pm$ 3.52
4	46	10.3 $\pm$ 4.26	45	12.2 $\pm$ 7.05	27	7.3 $\pm$ 2.61	36	8.2 $\pm$ 4.93
7	46	9.4 $\pm$ 2.90	46	10.2 $\pm$ 4.65	27	8.1 $\pm$ 5.33	30	8.2 $\pm$ 5.29
14	42	8.6 $\pm$ 3.31	43	10.2 $\pm$ 5.83	22	7.7 $\pm$ 3.71	30	8.5 $\pm$ 5.02
21	21	8.4 $\pm$ 4.95	28	10.1 $\pm$ 5.40	13	7.0 $\pm$ 2.92	18	8.4 $\pm$ 4.97

N = Number of subjects

Pulse and Temperature

There were no notable differences with respect to mean pulse (bpm) or temperature ($^{\circ}$ F) between subjects receiving Lot 2R-85 and Lot 3-85 (Table 29). All subjects had pulse rates within normal ranges, defined as 60 to 100 bpm. No subjects demonstrated fever, defined as temperature $>100^{\circ}$ F; however, AEs reported by the subjects may seem to contradict this. Fever, as reported by the subjects, included the definition of "feeling feverish," which is a subjective measurement.

Table 30. Maximum Pulse and Temperature Measurements

Evaluation Day	Pulse (bpm)				Temperature ($^{\circ}$ F)			
	Lot 2R-85		Lot 3-85		Lot 2R-85		Lot 3-85	
	N	Mean $\pm$ SD	N	Mean $\pm$ SD	N	Mean $\pm$ SD	N	Mean $\pm$ SD
0	41	73.7 $\pm$ 8.56	43	73.8 $\pm$ 9.55	47	98.1 $\pm$.98	45	97.8 $\pm$.95
1	47	73.5 $\pm$ 10.56	47	75.7 $\pm$ 10.47	47	98.0 $\pm$.76	47	98.2 $\pm$.76
2	46	74.3 $\pm$ 10.42	47	75.0 $\pm$ 10.05	46	98.2 $\pm$.62	47	98.2 $\pm$.77
4	46	75.5 $\pm$ 10.82	45	74.5 $\pm$ 10.11	44	98.4 $\pm$.66	45	98.3 $\pm$.70
7	47	74.8 $\pm$ 10.36	47	73.0 $\pm$ 10.46	47	98.2 $\pm$.66	47	98.0 $\pm$.82
14	46	74.1 $\pm$ 9.77	47	72.9 $\pm$ 9.10	46	98.2 $\pm$.69	47	97.9 $\pm$.76
21	21	77.2 $\pm$ 10.94	22	71.8 $\pm$ 8.02	21	98.5 $\pm$.82	23	98.3 $\pm$.68

N = Number of subjects

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9.3.2 Protocol 87-4, Log A-4706: Evaluation of New Lots of a Tularemia Vaccine, Protocol A: Initial Assessment of the Safety of *Francisella tularensis* Vaccine, Live, TSI-GSD 213, Lot 1R-85

Because the laboratory database was shared among SIP clinical studies and included tests not specific to this protocol, only selected tests were analyzed. The number of subjects with laboratory results above the established reference range is listed in Table 30. The number of subjects with above normal HCT, creatinine, HGB, platelets (PLT), and WBC is nearly identical in the vaccine and placebo groups.

Table 31. Laboratory Values above Normal Limits at Any Time Point and Latest Day of Resolution for Vaccine and Placebo Groups

Laboratory Test and Normal Range	Vaccine			Placebo		
	N	%	Resolution by Day	N	%	Resolution by Day
HCT (males 39.5 - 50.4%) (females 34.6 - 45.7%)	0	0	N/A	1	2.9	2
Creatinine 0.6 - 1.4 mg/dL	2	5.9	1	2	5.7	62
HGB (males 13.2 - 17 g/dL) (females 11.6 - 15.1 g/dL)	2	5.9	1	1	2.9	1
PLT 150 - 466 x 10 ³ /mm ³	1	2.9	44	1	2.9	2
WBC 3.2 - 10.8 x 10 ³ /mm ³	3	8.8	53	3	8.6	1

N = Number of subjects

HCT = Hematocrit

PLT = Platelet Counts

HGB = Hemoglobin

WBC = Leukocyte Count

Blood, Skin, and Throat Cultures

Growth of *F. tularensis* was detected within skin cultures from 2 subjects on Day 0 (Subject 2145) and Day 28 (Subject 2242) postvaccination, confirmed by slide agglutination. Assays on blood and throat cultures were negative for growth of *F. tularensis*.

Subjects with laboratory results below the reference range are listed in Table 31. Below reference ranges for HCT, HGB, and PLT are nearly identical between the vaccine and placebo groups.

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Table 32. Laboratory Values below Normal Limits at Any Time Point and Latest Day of Resolution for Vaccine and Placebo Groups

Laboratory Test and Normal Range	Vaccine			Placebo		
	N	%	Resolution by Day	N	%	Resolution by Day
HCT (males 39.5 - 50.4%) (females 34.6 - 45.7%)	5	14.7	35	7	20.0	14
Creatinine 0.6 - 1.4 mg/dL	0	0	N/A	0	0	N/A
HGB (males 13.2 - 17 g/dL) (females 11.6 - 15.1 g/dL)	4	11.8	51	4	11.4	59
PLT 150 - 466 x 10 ³ /mm ³	2	5.9	1	2	5.7	55
WBC 3.2 - 10.8 x 10 ³ /mm ³	1	2.9	1	0	0	N/A

N = Number of subjects

HCT = Hematocrit

PLT = Platelet Counts

HGB = Hemoglobin

WBC = Leukocyte Count

Biological Reactions and Vital Signs

Temperature (°F), erythema (mm), induration (mm), and blood pressure (mmHg) were among the vital signs measured and recorded from Day 0 to Day 33.

Temperature and Blood Pressure

A mixed model ANOVA was performed on the temperature data at Day 0 to Day 13 postvaccination, the period of time when adequate data were available. Two subjects (2181 and 9020) experienced a fever, as defined as temperature $\geq 100^{\circ}\text{F}$. The period of elevation varied from 2 days (Subject 2181) to 7 days (Subject 9020). A T_{max} of 102.2°F on Day 14 and 101.6°F on Day 3 were recorded for the 2 subjects, respectively. Subject 9020 was later diagnosed with Hodgkin's Disease, which was suspected to have been present prior to vaccination and the cause of the increase in temperature.

Erythema and Induration

A mixed model ANOVA was performed on the maximum measured erythema and induration data at Day 0 to 13 postvaccination, when available. Only maximum erythema differed between treatments ($p=0.0025$) with the greatest difference at Day 2 (vaccine 9.1 mm; placebo 3.9 mm). Maximum measured induration may also have been affected but did not reach a statistical significance due to the low number of subjects.

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9.4 Aerosol Challenge Studies Laboratory Data

9.4.1 Protocol 67-1: Respiratory *Pasteurella (Francisella) tularensis* in Man

Again, reference ranges for laboratory results from 1966 were not available so surrogates from a subsequent study (Protocol 87-4) were used. Laboratory tests conducted were not protocol-specific (the database was shared among multiple SIP investigational protocols); hence, only selected tests were analyzed. WBC count outside the established reference range (3.2 to $10.8 \times 10^9/L$) was expected and was seen in 8 subjects (7 virulent-challenge, 1 placebo control). Values returned to normal limits within 2 to 5 days, corresponding with the administration of streptomycin. Maximum WBC was seen in Subject 9468 ($17.2 \times 10^9/L$ and $17.5 \times 10^9/L$ on postexposure Days 5 and 6, respectively). Out-of-reference range values for other laboratory tests were unremarkable.

Throat Culture Studies

Throat cultures taken on Day -10 contained normal flora in 7 study subjects. Throat culture from 1 control subject (9471) contained isolated *E. coli* while the cultures from 1 control subject (9466) and 1 study subject (9468) contained isolated *Staphylococcus aureus*. The protocol did not require postchallenge throat cultures to be obtained.

Vital Signs

T_{max} measured in degrees Fahrenheit ($^{\circ}F$) and pulse (bpm) were the vital signs measured and recorded postchallenge. Fever was defined as a temperature measurement $>100^{\circ}F$. Temperature measurements ranged from $98.6^{\circ}F$ to $104.0^{\circ}F$ and occurred in all virulent-challenge subjects. None of the control subjects had a $T_{max} >100^{\circ}F$. Five subjects reached T_{max} at Day 4 (mean temperature $103.1^{\circ}F \pm 0.85^{\circ}$, range 101.4° to $104.0^{\circ}F$), whereas 1 subject peaked at Day 3 (T_{max} $103.8^{\circ}F$), and 2 subjects peaked at Day 5 (103.4° and $103.2^{\circ}F$). Pulse and temperature measurements were recorded daily from Day 0 to Day 13 postchallenge.

Statistical tests were not possible due to the small sample size of the control group.

All but 1 control subject had a pulse rate within the acceptable range of 60 to 100 bpm. Mean pulse rates for control subjects ranged from 63 to 102 bpm. Seven virulent-challenge subjects (50%) had pulse rates outside of the acceptable range with the maximum rate recorded of 136 bpm (mean pulse rate range 72.5 to 111.5 bpm).

Body Weight

Body weight measured as part of the task performance component of the study yielded no remarkable results and no trends were detected in either group ($p = 1.00$). Body height measurements were not consistently recorded. Other task performance data that may have been collected were not available.

9.4.2 Protocol 65-13: Evaluation of Storage Stability of Living Vaccine Strain (LVS) of *Pasteurella tularensis* and Protocol 65-13A: Evaluation of Metabolic Changes in Immunized Subjects Exposed to Infectious Doses of *P. tularensis*

Again, reference ranges for laboratory results from 1965 were not available so surrogates from a subsequent study (Protocol 87-4) were used; however, only selected tests were analyzed. Most out-of-reference range results occurred in unvaccinated control subjects. Postexposure levels of HCT (reference range: 39.5% to 50.4%) for 2 control subjects in the low-dose challenge group were considered out-of-reference range but were fairly mild (51% and 52%).

HGB levels (reference range: 13.2 g/dL to 17.0 g/dL) were considered below the reference range for 1 low-dose challenge Lot 2 subject, 2 high-dose challenge Lot 4 subjects, and 2 high-dose challenge control subjects. Erythrocyte sedimentation rate (ESR) (reference range: 0.0 mm/hr to 20.0 mm/hr) was above reference range on 2 low-dose challenge Lot 2 and control subjects, 1 high-dose challenge Lot 2 subject, 3 high-dose challenge Lot 4 subjects, and 1 high-dose challenge control subject. The maximum recorded ESR was 45 mm/hr, all high-dose challenge Lot 4 subjects.

All 6 control subjects, regardless of challenge dose, and all high-dose challenge Lot 2 subjects had recorded WBC counts outside the established reference range of $3.2 \times 10^9/L$ to $10.8 \times 10^9/L$. The maximum recorded WBC count was $13.3 \times 10^9/L$. None of the low-dose challenge subjects (Lot 2 or Lot 4) nor any high-dose challenge Lot 4 subjects had recorded WBC counts outside the established reference range.

Temperature and Pulse Rate

Temperature (°F) and pulse rate (bpm) were routinely measured. All subjects, regardless of challenge dose or vaccine lot received (including unvaccinated controls), had a recorded temperature $>100.0^\circ\text{F}$ at some point postchallenge; however, all temperatures resolved spontaneously and without sequelae. Temperature measurements ranged from 100.0°F to 105.2°F (Subject 9364, a high-dose challenge, unvaccinated control). A subject's T_{max} was generally found to occur on Day 3 although some subjects had a T_{max} recorded at Day 2 or Day 4.

Pulse rates over 100 bpm were recorded most frequently on Days 4, 8, and 9 for low-dose challenge Lot 2 subjects; Days 2 and 3 for high-dose challenge Lot 2 subjects; Days 2, 3, and 8 for low-dose challenge Lot 4 subjects; Days 2, 3, and 9 for high-dose challenge Lot 4 subjects; Days 3, 4, 9, 10, and 11 for low-dose challenge unvaccinated control subjects; and Days 2, 3, 9, and 10 for high-dose challenge unvaccinated control subjects. After peaking on these days, pulse rates began the descent to normal (<100 bpm).

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Pharyngeal Washes and Throat Cultures

All subjects (including unvaccinated controls) had positive throat cultures prior to aerosol challenge; however, none were positive for tularemia. Throat cultures were not obtained postchallenge.

Clinical Safety (Protocol 65-13A)

Again, reference ranges for laboratory results from 1965 were not available so surrogates from a subsequent study (Protocol 87-4) were used; however, only selected tests were analyzed.

Postexposure levels of HCT (reference range: 39.5% to 50.4%) for only 1 subject in the high-dose challenge Lot 4 group were considered out-of-reference range but was fairly mild (51%). HGB levels (reference range: 13.2 g/dL to 17.0 g/dL) were considered below the reference range for 1 low-dose challenge Lot 4 subject and 2 high-dose challenge Lot 2 subjects.

ESR rates (reference range: 0.0 mm/hr to 20.0 mm/hr) were above reference range on all 4 high-dose challenge subjects, regardless of vaccine lot received. WBC count was not measured. Likewise, there is no indication that urine was collected or measured or that stool markers were evaluated as per the study protocol.

Temperature and Pulse Rate

Rectal temperature (°F) and pulse rate (bpm) were recorded routinely while the subject was hospitalized. All subjects, regardless of challenge dose or lot vaccinated (including unvaccinated controls), had a recorded temperature >100.0°F at some point postchallenge.

Temperature measurements ranged from 100.0°F to 104.2°F (Subject 9355, a high-dose challenge Lot 2 subject). Subjects in the low-dose challenge group (Lot 2 or Lot 4) were found to have a T_{max} occurring on Days 2 through 5. T_{max} for subjects in the high-dose challenge group (Lot 2 or Lot 4) occurred on Days 2 through 7.

Pulse rates over 100 bpm were recorded only on Days 2 and 3 in high-dose challenge Lot 2 subjects, after which pulse rates began a steady descent to normal (<100 bpm) by Day 15 postexposure. None of the subjects in the low-dose challenge (Lot 2 or Lot 4) or high-dose challenge Lot 4 group had a recorded pulse rate >100 bpm.

Pharyngeal Washes and Throat Cultures

Throat cultures were to be done only when considered by the clinician to be necessary and procedures were unclear as to when pharyngeal washes should be obtained.

9.5 Skin Test Study Laboratory Data

9.5.1 Protocol 75-2: Evaluation in Volunteers of the A-RFC Test as an Assay for Previous Immunization to Tularemia

Hematocrit recorded on Day -3 was within normal limits (reference range: 39.5 to 50.4 males; 34.6 to 45.7 females) for all subjects. Results for other laboratory tests, including lymphocytes, eosinophils, monocytes, and neutrophils were listed but not further evaluated. Laboratory tests were not performed consistently throughout the study.

Induration

None of the five tularemia-naïve control subjects had measurable induration at the test site after administration of the Foshay skin test antigen. Four previously vaccinated subjects (Subjects 1492, 1526, 174, and 428), however, had delayed cutaneous hypersensitivity reactions to the Foshay skin antigen test at the skin test site at 48 and 72 hours after administration indicating a positive reaction. The maximum induration for these subjects measured between 5 x 6 mm and 20 x 22 mm. A positive skin reaction to the skin test antigen was defined as a subject with a measurement of induration ≥ 0.5 cm at the skin test site.

No local or systemic side effects occurred after the skin test was administered to the 2 subjects enrolled in the supplemental study. Data show that both subjects had a positive skin test response at 48 hours; however, the induration measurement was not recorded.

10 Additional Human Safety Information

There is no additional human safety information.

11 Special Pharmacologic Properties

The tularemia vaccine (TSI-GSD or NDBR 101) product has no special pharmacologic properties other than the property of principal interest.

12 Summary and Conclusions

There are two tularemia vaccine products: NDBR 101 and TSI-GSD 213, both of which are live and attenuated. The manufacturing process has been summarized previously in this report.

This report reviews safety data from 12 clinical trials. In these trials, a total of 1,270 subjects were exposed to tularemia, either by vaccination, aerosol challenge, or skin test. Most subjects were male (88%), white (85%), and between the ages of 20 and 29 (46%). Vaccination was a single dose of approximately 0.1 mL vaccine product placed on the skin arm and pierced 15 to 30 times with a bifurcated needle (multiple puncture technique). Aerosol challenge exposed subjects to a range of up to 36,368 virulent *F. tularensis* organisms using a modified Henderson apparatus. The skin test was a single dose (0.1 mL) of freshly reconstituted Foshay skin test antigen (1:1000 dilution of phenol-killed Foshay vaccine) injected IC into the forearm.

The analysis in this report is primarily based on recorded AEs. An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational drug (vaccine) that does not necessarily have a causal relationship with this treatment. An AE, therefore, can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product (e.g., tularemia vaccine, aerosol, or skin test antigen) whether or not causally related.

There were 1,119 AEs reported among the 1,270 subjects enrolled in the 12 studies. The percentages of AEs reported among the NDBR 101 and TSI-GSD 213 products appear to be relatively equal (42% vs. 44%, respectively, across all studies); however, there were substantially more subjects in the NDBR 101 studies than the TSI-GSD 213 studies (1,064 vs. 163, respectively). There were 468 AEs reported among the 1,064 subjects vaccinated by an NDBR 101 product and 493 AEs reported among the 163 subjects vaccinated by a TSI-GSD 213 product. The smaller number of AEs reported in the NDBR 101 studies may be because the NDBR 101 product was less reactogenic than the TSI-GSD 213 product or because data collection methods were more thorough in the TSI-GSD 213 studies. The TSI-GSD 213 studies were conducted for the most part after the NDBR 101 studies when reporting guidances became more stringent (i.e., Good Clinical Practices).

There were 158 AEs reported among the 32 subjects in the aerosol challenge studies accounting for 14% of the total number of AEs reported across all studies. No AEs were reported by subjects in the skin test study.

The safety profile of the tularemia vaccine is mainly characterized by typical vaccination reactions. Of the 12 body systems, 53% of the AEs were in the Skin and Appendages body system with papule (13%), lesion and lesion at injection site (11%), and pruritus

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(7%) being the top 3 AEs reported. AEs in the Body as a Whole, Hemic and Lymphatic, and Musculoskeletal body systems accounted for 21%, 8%, and 6.3%, respectively, with the top AEs reported being headache (7.4%), fever (4.7%), malaise (4.7%), lymphadenopathy (8%), and myalgia (4.4%). The remaining 8 body systems accounted for less than 12% of the recorded AEs: Cardiovascular (no AEs reported), Digestive (0.4%), Eyes, Ears, Nose, Throat (4%), Gastrointestinal (3.5%), Metabolic and Nutritional (no AEs reported), Nervous (1.2%), Respiratory (2.4%), and Urogenital (0.1%).

Two SAEs, defined as resulting in death, a life-threatening AE, an inpatient hospitalization, a persistent or significant disability/incapacitation, or a congenital anomaly/birth defect, were documented, one in Protocol 87-4 and the other in Protocol 87-9. The subject in Protocol 87-4 was hospitalized with fever and diffuse adenopathy but was later diagnosed with Hodgkin's disease, nodular sclerosing variety, that was most likely present prior to the subject's enrollment in the study. It has, therefore, been determined that this SAE was unrelated to the administration of the vaccine. No safety reports were required to be submitted to FDA.

The subject in Protocol 87-9 was seen as an outpatient in the emergency room complaining of eye pain and loss of vision. The subject had been vaccinated 4 years prior to the AE, was enrolled in multiple protocols, and was also predisposed to HLA-B27-associated uveitis because of an autoimmune condition. The causal relationship of the SAE reported for the Protocol 87-9 subject was thoroughly reviewed and was conclusively determined unlikely to be related to the administration of the vaccine. No subjects developed an actual or modified form of the natural disease, and no systemic allergic reactions or GBS were attributed to live, attenuated tularemia vaccine(s).

LFT data were collected in only four of the studies. None of the 20 subjects vaccinated with Lot 4 (Part I of Protocol 68-4) had an LFT out of the established reference range and only 2 subjects (10%), both noncontrols in the high-dose challenge group, had ALT and AST values outside the established reference range. Data available on 121 subjects vaccinated with NDBR 101, Lot 11 (Protocol 87-9) showed 22 subjects (18.2%) had elevated ALT values and 16 subjects (13.2%) had elevated AST levels. Most of the elevated readings were short-lived as elevated ALT values for 14 of the 22 subjects (64%) and elevated AST values for 13 of the 16 subjects (81%) returned to within normal limits at Day 1.

In the TSI-GSD 213 studies, data were not available on all 47 subjects in each treatment group; however, elevated ALT levels were seen in 5 of 42 subjects (10.6%) vaccinated with Lot 2R-85 and in 2 of 45 subjects (4.3%) vaccinated with Lot 3-85 (Protocol 91-9). Elevated AST levels were reported in 5 of 42 subjects (10.6%) vaccinated with Lot 2R-85 and 1 of 46 subjects (1.6%) vaccinated with Lot 3-85. In Protocol 87-4, elevated ALT levels were seen in 9 of 34 subjects (26.5%) vaccinated with TSI-GSD 213, Lot 1R-85 and in 6 of 35 subjects (17.1%) given placebo. Elevated AST levels were also seen in 12

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of 34 subjects (35.3%) vaccinated with Lot 1R-85 and in 11 of 35 subjects (31.4%) given placebo.

In summary, the tularemia vaccine was well tolerated in healthy adult volunteers as evidenced by the low number of reported AEs and by the number of expected vs. unexpected AEs. Likewise, aerosol exposure and skin test exposure did not cause an inordinate number of unexpected AEs.

13 References

1. Francis E. Deer-fly fever, or Pahvant Valley Plague. A disease of man of hitherto unknown etiology. *Public Health Rep* 1919;34:2061-2062.
2. Penn RL. *Francisella tularensis* (tularemia). In: Mandell GL, Douglas RG, Bennett JE, eds. *Principles and Practices of Infectious Diseases*, 4th edition. New York: John Wiley and Sons, pp 2060-2067.
3. Sanders CV et al. Analysis of 106 cases of tularemia. *J Louisiana State Med Soc* 1968;120:391-393.
4. Cox SK et al. Tularemia. An analysis of 25 cases. *Mod Med* 1981;78:10-14.
5. Ohara Y et al. Clinical manifestations of tularemia in Japan-analysis of 1,355 cases observed between 1924 and 1987. *Infection* 1991;19:14-17.
6. Evans ME et al. Tularemia: One 30-year experience with 88 cases. *Medicine* 1985;64(4):251-269.
7. Jacobs RF. Tularemia. In: Fauci AS, Braunwald E, Isselbacher KJ et al, eds. *Harrison's Principles of Internal Medicine* 1998. 14th edition, Vol 1, p 971.
8. Bartelloni PJ. Clinical studies of attenuated tularemia vaccine. Commission on Epidemiological Survey. *Annual Report to the Armed Forces Epidemiological Board*. Fiscal Year 1969:179-185.
9. Eigelsbach HT, Downs CM. Prophylactic effectiveness of live and killed tularemia vaccines. *J Immunol* 1961;(87):415-425.
10. *Mortality and Morbidity Weekly Report*. October 26, 1984 / 33(42);601-2.

14 Appendix

14.1 Documented Etiology and Narratives for Subjects with Elevated LFTs Enrolled in Protocol 87-9 (NDBR 101, Lot 11)

Table 33. Etiology of Subjects with Liver Function Test Elevations (Protocol 87-9)

Subject Demographics			Etiology/Possible Contributing Factors
ID	Age	Sex	
165	23	M	Baseline GGT elevation; history of chronic back pain
202	24	M	Baseline ALT elevation; history of reduction diet
334	39	M	Baseline ALT elevation; history of HCV
463	45	M	Baseline ALT & GGT elevation; significant use of alcohol
726	42	M	Baseline ALT & GGT elevation; Hepatitis A virus (HAV) infection; significant use of alcohol
761	39	M	Baseline GGT elevation; significant use of alcohol
962	43	M	Baseline ALT & GGT elevation; obstructive pattern of LFTs, gallstones; OTC antacids
2194	45	M	Study record not available
116	37	M	Baseline ALT elevation; no documented etiology
1575	50	M	Gastroesophageal reflux disease; pre-existing elevated lactic dehydrogenase (LDH); alcohol user
1960	23	M	Alcohol user
481	44	M	Baseline ALT elevation; post-HBV infection prior to vaccination
1030	31	M	No documented etiology
107	53	M	Zocor [®] prior & concomitant medicine
1286	37	M	Baseline LDH elevation; alcohol user; stomach problems
160	58	M	Ongoing treatment for hyperparathyroidism
1720	20	F	Post-HBV infection
196	47	M	Baseline ALT elevation; no documented etiology
2262	38	M	Hypercholesterolemia; hepatitis; cytomegalovirus
335	45	M	History of LFT elevation; diuretic pill thought to be the contributing factor
517	48	M	Baseline fasting blood sugar (FBS) elevation; alcohol use
519	53	M	History of AST elevation; obesity
716	57	M	History of ALT elevation; no documented etiology
773	31	M	Baseline ALT & AST elevation; occasional alcohol use
815	40	M	Baseline ALT elevation; history of "stomach problems"
847	30	M	Baseline ALT & AST elevation; history of chronic stomach problems; alcohol use
902	31	M	Baseline ALT elevation; history of elevated LFTs; no documented etiology
919	32	M	History of ALT & AST elevation; significant history of elevated cholesterol, triglycerides, and LFTs

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Reference range: ALT 0-50 IU/L; AST 10-42 IU/L

Subject 165 (a 23-year-old Hispanic male, vaccinated at USAMRIID) had baseline elevations of gamma-glutamyl transferase (GGT) that persisted to Day 14 postvaccination. Mild elevations of ALT were detected for 8 months following vaccination and resolved by Month 10 (range 71 IU/L to 96 IU/L). No mention of the suspected cause was made in the subject's medical record; however, the subject had a history of chronic back pain and may have self-administered analgesics.

Subject 202 (a 24-year-old Asian male, vaccinated at an extramural site) had a baseline elevation of ALT (63 IU/L that dipped at Day 294 to 57 IU/L and rose again on Day 847 [100 IU/L; AST 46 IU/L]). The Special Immunizations Program (SIP) placed the subject on HOLD for any further vaccinations until the LFTs could be repeated and the subject's primary care physician could be consulted. Once re-tested, the subject's ALT decreased to 87 IU/L (with an AST of 35 IU/L) and by Day 1275, the subject's ALT had decreased to 77 IU/L. The subject provided a letter from his primary care physician stating that he was cleared for vaccinations in SIP and explained the subject was on a reduction diet. LFTs were to be repeated in 3 months.

Subject 334 (a 39-year-old white male, vaccinated at USAMRIID) had a baseline elevation of ALT persistent through Day 226 (range 89 IU/L to 128 IU/L). Antibody to HCV was detected in serum obtained 6 months prior to vaccination; therefore, elevated transaminase values were suspected as being pre-existing. The subject was started on interferon 1 year after receiving tularemia vaccine.

Subject 463 (a 45-year-old white male, vaccinated at USAMRIID) had a baseline transaminase elevation recorded 4 years prior to vaccination with tularemia vaccine. GGT was mildly elevated on Day 0 and continued to rise over the next 2 years. At Day 28, the subject's ALT was mildly elevated (72 IU/L). The subject was diagnosed as an alcohol abuser 1 year after receiving the vaccine. It is believed that the elevated transaminase was a pre-existing condition resulting from the regular, significant use of alcohol.

Subject 726 (a 42-year-old white male, vaccinated at USAMRIID) had significant baseline ALT and GGT elevations recorded 4 years prior to vaccination with tularemia vaccine (range: 56 IU/L to 102 IU/L). Labs were collected annually, and mild elevations of ALT were noted for 3 years after vaccination. GGT was significantly elevated the first 2 years. A notation in the subject's medical record dated February 2, 1990 indicated a history of HAV infection and annotation that he was trying to cut down on alcohol because he was told he had a "liver problem." It is suspected that HAV, rather than the vaccine, was the cause of the elevated transaminase.

Subject 761 (a 39-year-old white male, vaccinated at USAMRIID) had a minor elevation of GGT prior to tularemia vaccination. LFTs were mildly elevated on several occasions for the next 30 days, with ALT ranging from 68 IU/L at Day 1 to 64 IU/L at Day 7

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postvaccination. The subject admitted to drinking an average of 6 alcoholic drinks per month and disclosed a history of arthritis but no routine medications. LFTs returned to normal levels and remained so for the next 2 years while in the study.

Subject 962 (a 43-year-old black male, vaccinated at USAMRIID) had a baseline elevation of ALT (67 IU/L) recorded 2 years prior to tularemia vaccination that, along with elevated GGT on Day 0, persisted over the next 2 years. The Investigator documented in the subject's medical record a history of obstructive pattern of the LFTs and gallstones that were verified through a CT scan of the abdomen. The subject also frequently complained of abdominal pain and took over-the-counter antacids.

Subject 2194 (a 45-year-old white male, vaccinated at USAMRIID) did not have an elevation of ALT until Day 197 (ALT = 103 IU/L; AST = 49 IU/L). All other labs were within normal limits. The study record for this subject is not available.

Subject 116 (a 37 year-old white male, vaccinated at an extramural site) had a baseline (Day 0) ALT elevation of 53 IU/L. At Day 198, the ALT had elevated to 56 IU/L. No etiology was noted in the subject's study record.

Subject 1575 (a 50-year-old white male, vaccinated at an extramural site) had an elevated ALT (72 IU/L) at Day 342 that persisted for 2 years. The subject reported alcohol usage and difficulty with gastroesophageal reflux disease (GERD). This subject's recorded lactic dehydrogenase (LDH) was also significantly elevated (601 IU/L) and had been persistently elevated from as far back as 5 years prior to receiving tularemia vaccination.

Subject 1960 (a 23-year-old Hispanic male, vaccinated at an extramural site) had baseline ALT and AST within normal limits that rose on Day 259 to 91 IU/L and 43 IU/L, respectively. The subject admitted to a history of alcohol use and all repeat labs were within normal limits. No etiology was given for the isolated elevation.

Subject 481 (a 44-year-old Asian male, vaccinated at an extramural site) had a mild baseline elevation of ALT (58 IU/L). By Day 281, the subject's ALT was 78 IU/L (LDH = 629 IU/L). Review of the study record revealed the subject was post-HBV with positive core HBV antibody prior to tularemia vaccination.

Subject 1030 (a 31-year-old white male, vaccinated at USAMRIID) had a mild elevation of ALT at Day 28 and Day 111 (64 IU/L and 57 IU/L, respectively). Additional information regarding the elevated LFTs are not available in the subject's study record.

Subject 107 (a 53-year-old white male, vaccinated at USAMRIID) had a mild elevation of AST (44 IU/L) at Day 84 that fell to within normal limits at Day 181. The subject had been taking Zocor[®] prior to and concomitantly with vaccination. All other labs were within normal limits at baseline and throughout the study. There is no other etiology, therefore, the elevated AST is believed to be a spurious finding.

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Subject 1286 (a 37-year-old white male, vaccinated at USAMRIID) had a mild elevation of AST (46 IU/L) at Day 12. Upon further examination of his medical record, it was discovered that the recorded AST levels in this subject had been elevated consistently for 4 years prior to tularemia vaccination (range 37 IU/L to 51 IU/L). The subject also had a documented history of elevated LDH (range 598 IU/L to 648 IU/L) for 4 years prior to tularemia vaccination. AST was within normal limits by Month 10, whereas the LDH remained high (613 IU/L). The subject's study record revealed a history of stomach problems and alcohol use.

Subject 160 (a 58-year-old white male, vaccinated at USAMRIID) had elevated ALT and AST on Day 243 (70 IU/L and 46 IU/L, respectively). On Day 251 ALT and AST levels had begun to drop (62 IU/L and 39 IU/L, respectively). No other lab information was available on this subject. This subject's study record indicated ongoing treatment for hyperparathyroidism although there is no mention of elevated LFTs.

Subject 1720 (a 20-year-old white female, vaccinated at USAMRIID) had a mild elevation of AST (44 IU/L) on Day 176. All other labs were within normal limits with the exception of positive core antibody to HBV, indicating previous exposure, recovery, and relationship to reported AST elevations.

Subject 196 (a 47-year-old white male, vaccinated at USAMRIID) had a baseline elevation of ALT (90 IU/L) and LDH (582 IU/L). At Day 201, ALT had dropped to 54 IU/L. There is no narrative in the subject's study record and no documented etiology for baseline condition.

Subject 2262 (a 38-year-old white male, vaccinated at USAMRIID) had an ALT elevation (54 IU/L, 59 IU/L) on Days 300 and 329, respectively. AST was also elevated on Day 329. The subject began Lovastatin[®] therapy for long-term hypercholesterolemia 2 years prior to tularemia vaccination. The subject also developed hepatitis due to cytomegalovirus 1 year prior to tularemia vaccination. There were no prior LFTs documented in the subject's study record.

Subject 335 (a 45-year-old white male, vaccinated at USAMRIID) had a mild AST elevation (44 IU/L) on Day 69 and the subject's study record documents a history of LFT elevations. Documentation 3 months prior to tularemia vaccination by the subject's primary care physician indicated LFTs had returned to normal from the prior week citing the discontinuation of a fluid pill.

Subject 517 (a 48-year-old white male, vaccinated at USAMRIID) had no baseline ALT elevation, but a mild ALT elevation (52 IU/L) on Day 140 postvaccination. The subject reported occasional alcohol usage on his medical history form. Fasting blood sugar (FBS) was also elevated at baseline and the subject was diagnosed with diabetes 2 years postvaccination.

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Subject 519 (a 53-year-old white male, vaccinated at USAMRIID) had a mild AST elevation (43 IU/L) on Day 28. The subject's study record documents a history of AST elevations ranging from 45 IU/L to 53 IU/L. LFTs were also documented to be within normal limits on 3 past occasions. The subject reported a past medical history of obesity and denied alcohol use.

Subject 716 (a 57-year-old white male, vaccinated at USAMRIID) had a mild elevation of ALT (51 IU/L) on Day 2 postvaccination. Further investigation of the subject's medical record revealed a past history of elevated ALT (55 IU/L). Etiology was not named or discussed.

Subject 773 (a 31-year-old white male, vaccinated at USAMRIID) had a mild elevation of ALT (51 IU/L) and AST (43 IU/L) at Day -21. ALT was also elevated on Day 160 (47 IU/L) but had dropped from prevaccination levels. The subject's study record revealed a history of occasional alcohol use prior to tularemia vaccination.

Subject 815 (a 40-year-old white male, vaccinated at USAMRIID) had a baseline elevation of ALT (52 IU/L at Day -15 and 60 at Day -6). ALT on Day 343 was 51 IU/L. Documentation from the subject's medical and study records indicate a past medical history of "stomach problems" pre- and post-tularemia vaccination.

Subject 847 (a 30-year-old white male, vaccinated at USAMRIID) had LFT elevations 18 months prior to tularemia vaccination (ALT 71 IU/L and AST 51 IU/L in January 1992; ALT 88 IU/L and AST 53 IU/L in January 1993). At Day 174, the subject's ALT was 71 IU/L and AST was 45 IU/L. ALT on Day 187 postvaccination was 77 IU/L. Documentation from the subject's study record indicates a past medical history of chronic stomach problems (date of onset 1989) and alcohol use.

Subject 902 (a 31-year-old white male, vaccinated at USAMRIID) had a mild baseline ALT elevation (50 IU/L) on Day -14 that continued to be elevated on Day 14 post tularemia vaccination (52 IU/L). Documentation from the subject's study record indicates prior LFT elevations existed in each of 3 years prevaccination (67 IU/L in 1991, 57 IU/L in 1992, 52 IU/L in 1993, and 56 IU/L in 1994).

Subject 919 (a 32-year-old white male, vaccinated at USAMRIID) had documented LFT elevations (ALT = 118 IU/L, AST = 79 IU/L, LDH = 559 IU/L) in his study record 3 years prior to tularemia vaccination. Subsequent LFTs were within normal limits on at least 4 occasions; however, ALT was 62 IU/L in 1991, 54 IU/L in 1994, and 57 IU/L in 1996 (Date of vaccination: 04/07/93). No etiology was documented in the study record; however, the subject had a significant history of elevated cholesterol, triglycerides, and LFTs. The subject was referred to his primary care physician for treatment.

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14.2 Documented Etiology and Narratives for Subjects with Elevated LFTs Enrolled in Protocol 91-9 (TSI-GSD 213, Lot 2R-85 and 3-85)

Table 34. Etiology of Subjects with Liver Function Test Elevations (Protocol 91-9)

Subject Demographics				Etiology/Possible Contributing Factors
ID	Age	Sex	Group	
9862	22	M	Lot 2R-85	History of creatine phosphokinase (CPK) elevations; weight lifter
10005	45	M	Lot 2R-85	Alcohol use during study
10175	32	M	Lot 2R-85	HCV; significant use of alcohol
10177	33	M	Lot 2R-85	No etiology documented
10182	30	M	Lot 2R-85	History of illicit drug use
10183	39	M	Lot 2R-85	Significant use of alcohol
10185	39	M	Lot 2R-85	No etiology documented
10004	31	M	Lot 3-85	No etiology documented
10204	32	M	Lot 3-85	Alcohol use; strenuous exercise

Reference range: ALT 0-50 IU/L; AST 0-50 IU/L

Subject 9862 (a 22-year-old white male, Lot 2R-85 group) had minor ALT elevations on Days 1, 2, 4, and 14 and minor AST elevations on Days 1 and 2 postvaccination. The subject denied ethanol abuse in his medical history. He is an avid weight lifter, and persistent mild to moderate creatine phosphokinase (CPK) elevations were noted, which had previously been reported and correlate with transaminase increases after strenuous exercise. His ALT/AST returned to normal by Day 7, with a minor elevation in ALT on Day 14. His CPK was normal by Day 14.

Subject 10005 (a 45-year-old white male, Lot 2R-85 group) had a single day of minor AST (no ALT) elevation on Day 4 postvaccination. The subject reported drinking between 2 and 3 beers during the first week after inoculation. By Day 7, AST for this subject had returned to normal limits.

Subject 10175 (a 32-year-old black male, Lot 2R-85 group) developed persistent elevations of both ALT and AST values initiating on Day 1 postvaccination and resolving on Day 291. HbsAg was negative at screening and contemporarily with enzyme elevations. Hepatitis B virus core IgM and hepatitis A virus IgM were negative. HCV antibodies were detected in serum obtained on Day 67. Retrospective evaluation of archived screening serum (Day -4) revealed hepatitis C antibodies; however, archived serum from 10 months prior to inoculation was negative. Thus, HCV seroconversion must have occurred at an unknown interval, but less than 10 months before TSI-GSD 213 inoculation. The relationship of HCV infection to the development of abnormal LFTs during the study seems uncertain since ALT and AST were normal at screening, but

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cannot be discounted. The subject also admitted to substantial use of alcohol subsequent to the death of a relative, and this may be a more likely contributor. The subject was followed long-term (145 days postvaccination) by clinicians at The Johns Hopkins Center for Immunization Research, and laboratory values for alkaline phosphatase (ALP) and bilirubin remained normal. The patient remained asymptomatic according to the PI's 1993 interim safety report.

Subject 10177 (a 33-year-old black male, Lot 2R-85 group) had a minor, transient elevated AST on Day 7.

Subject 10182 (a 30-year-old black male, Lot 2R-85 group) had minor ALT (but no AST) elevations on Days 1, 2, and 4. The medical record documented an admission of drug abuse in the recent past, stating that he used marijuana. However, there was no history or mention of alcohol abuse. LFTs returned to normal values by Day 7.

Subject 10183 (a 39-year-old black male, Lot 2R-85 group) developed minor elevations of ALT and AST that persisted from Day 14 to Day 64 postvaccination. He admitted to heavy alcohol use the day before sera were collected for laboratory tests. On subsequent visits, it was noted in the medical record that alcohol was detected on the subject's breath. His LFTs normalized by Day 70 and subsequently the subject was lost to follow-up.

Subject 10185 (a 39-year-old black male, Lot 2R-85 group) had a minor, transient elevated ALT on Day 14.

Subject 10004 (a 31-year-old black male, Lot 3-85 group) had minor ALT (no AST) elevations on Days 2, 7, and 14 with normal ALT on Day 4. There was no documented history of alcohol or drug abuse in the medical record nor any explanation from the PI.

Subject 10204 (a 32-year-old white male, Lot 3-85 group) had minor elevations of AST and ALT that began on Day 7 and returned to normal ranges by Day 14. It was reported that he had been exercising strenuously in the gym 3 days prior to blood draw on Day 7. Medical history documented an admission of an intake of up to two alcohol drinks per week.

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14.3 Documented Etiology and Narratives for Subjects with Elevated LFTs Enrolled in Protocol 87-4 (TSI-GSD 213, Lot 1R-85)

Table 35. Etiology of Subjects with Liver Function Test Elevations (Protocol 87-4)

Subject Demographics				Etiology/Possible Contributing Factors
ID	Age	Sex	Group	
1987	19	M	1R-85	Significant alcohol use documented
2029	20	M	1R-85	Baseline bilirubin elevation; etiology not otherwise addressed
2074	20	M	1R-85	Etiology not addressed
2179	22	M	1R-85	Etiology addressed as "unknown"
2181	25	M	1R-85	Routine alcohol use documented
2193	30	M	1R-85	Etiology addressed as "unknown"
2213	22	M	1R-85	Routine alcohol use documented
2255	20	M	1R-85	Baseline AST elevation; routine alcohol use
2265	21	M	1R-85	Significant alcohol use documented
9007	26	M	1R-85	History of elevated ALT; within normal limits (WNL) by Day 11
9013	20	M	1R-85	LFTs WNL by Day 28; etiology assessed as related to vaccine
9016	20	M	1R-85	LFTs WNL by Day 28; etiology assessed as related to vaccine
9023	18	M	1R-85	Routine alcohol use documented
9025	24	M	1R-85	Routine alcohol use documented
9024	21	M	placebo	Significant alcohol use documented
9005 00X	20	M	placebo	Etiology not addressed
9026	20	M	placebo	Etiology not addressed
9027	21	M	placebo	Baseline bilirubin elevation; occasional alcohol use; etiology not otherwise addressed
9042	25	M	placebo	Etiology not addressed
9045	26	M	placebo	Etiology not addressed
9050	21	M	placebo	Etiology not addressed
9055	22	M	placebo	Routine alcohol use documented
9058	20	M	placebo	Etiology not addressed
9028	19	M	placebo	Etiology not addressed
9033	30	M	placebo	Occasional alcohol use documented
9035	21	M	placebo	Significant alcohol use documented
9056	24	M	placebo	Alcohol use documented

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Note: AST and ALT elevations are measured in IU/L, but in the interest of readability are omitted from the following narratives.

Vaccine Group: (N = 14)

Reference range: ALT 0-50 IU/L; AST 10-42 IU/L

Subject 1987 (a 19-year-old white male) had an elevation of AST on Day 7 (51), Day 158 (48), and Day 164 (90). AST and ALT were mildly elevated at Day 7 (AST 51; ALT 61) but were otherwise within normal limits. Elevations were attributed to the subject's admission of routine use of a 6 pack of beer per week on medical history form.

Subject 2029 (a 20-year-old white male) had a minor elevation of AST on Day 62 (44) and Day 283 (51). ALT was within normal limits. Subject had a baseline elevation of total bilirubin (1.6 mg/dL). Etiology was not addressed in the medical record.

Subject 2074 (a 20-year-old black male) had a minor elevation of AST on Day 1 (44) that fell to within normal limits by Day 2 (38) and remained normal at Day 4 (37). AST was mildly elevated on Day 7 (44) and Day 9 (48) then fell to within normal limits from Day 11 through Day 63. Documentation at Day 344 noted a mild AST elevation (43). Etiology was not addressed in the narrative notes. The subject denied alcohol use on the medical history form.

Subject 2179 (a 22-year-old black male) had an elevation of AST on Day 9 (84) and Day 11 (80). Mild elevations of ALT were recorded on Day 9 (56) and Day 11 (57), the etiology of which was documented as "unknown" in the medical record.

Subject 2181 (a 25-year-old white male) had a minor elevation of AST on Day 28 (48), Day 63 (52), and Day 210 (46). ALT was mildly elevated on Day 210 (65). The subject admitted to routine use of approximately 6 beers per week on the medical history form.

Subject 2193 (a 30-year-old white male) had mild elevations of AST on Day 4 (49) and Day 9 (44). ALT was elevated on Day 4 (78), Day 7 (87), Day 9 (104), Day 11 (71), and Day 14 (61). Etiology was assessed as "unknown."

Subject 2213 (a 22-year-old white male) had a minor elevation of AST on Day 9 (48). ALT was mildly elevated on Day 7 (53) and Day 14 (55) and within normal limits on Day -2 (50), Day 9 (48), Day 11 (45), and Day 28 (50). Etiology was attributed to the subject's admission of routine use of at least two 6 packs of beer per week.

Subject 2255 (a 20-year-old black male) had an elevation of AST on Day -1 (43), Day 4 (43), Day 9 (45), Day 11 (47), and Day 28 (68). Etiology was attributed to the subject's admission of routine use of approximately 2 beers per week on the medical history form.

Subject 2265 (a 21-year-old black male) had an elevation of AST on Day 103 (63). Etiology was attributed to the subject's admission of "significant" routine alcohol use, approximately one 6 pack per week, on the medical history form.

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Subject 9007 (a 26-year-old white male) had an elevation of AST noted on Day 62 (71). ALT was elevated on Day -2 (61), within normal limits on Day -1 (50), and elevated again on Day 2 (53), Day 4 (72), Day 7 (58), and Day 10 (54). ALT returned to normal by Day 11. Etiology was assessed as “uncertain” in the medical record; however, because elevations were documented prior to vaccination, they were most likely not due to the vaccine.

Subject 9013 (a 20-year-old white male) had an elevation of ALT on Day 7 (86), Day 10 (106), and Day 14 (52). Etiology was assessed as probably related to the vaccine. All LFTs were within normal limits by Day 28 and remained so through Day 55.

Subject 9016 (a 20-year-old white male) had an elevation of ALT on Day 1 (59), Day 2 (75), Day 4 (107), Day 5 (106), and Day 7 (103). Etiology was assessed as probably related to the vaccine. By Day 14, all had returned to within normal limits except gamma-glutamyl transferase (GGT) (50); by Day 28 all LFTs were within normal limits. There was a mild ALT elevation (57) noted again on Day 56. Subject was negative for Epstein-Barr virus (EBV), cytomegalovirus (CMV), hepatitis, erythrocyte sedimentation rate (ESR), renal failure (RF), antimicrobial antibodies, and antinuclear antibodies, leading the PI to surmise the elevations were caused by the vaccine. However, because the elevated LFTs returned to normal by Day 28 and began to rise again on Day 56, that conclusion may not be definitive.

Subject 9023 (an 18-year-old black male) had no LFT elevations while on the study measured at various timepoints from Day -15 through Day 222; however, the subject had an elevation of AST on Day 335 (269), Day 339 (144), Day 347 (90), and Day 364 (52) and an elevation of ALT on Day 335 (152), Day 339 (128), and Day 347 (93). The subject admitted to routine use of 2 beers per week on the medical history form. There appeared to be no temporal relationship of the LFT elevations to the vaccine.

Subject 9025 (a 24-year-old white male) had a minor elevation of AST on Day 206 (43), which was within normal limits on all other study days. Etiology was attributed to the subject's admission of routine use of several beers per week on the medical history form.

Placebo group (N = 13)

Reference range: AST 10-42 IU/L; ALT 0-50 IU/L

Subject 9024 (a 21-year-old white male) had one minor elevation of AST on Day 28 (48) and an elevation of ALT on Day -21 (61), Day 1 (51), Day 2 (57), Day 4 (51), Day 7 (69), Day 28 (121), and Day 35 (61). All other ALTs were within normal limits including those recorded on Day 15 (50) and Day 35 (61). The discharge summary states that blood had been drawn after the subject returned from convalescent leave during which the subject admitted to consuming “excessive” amounts of alcohol.

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Subject 900500X (a 20-year-old white male) had a mild elevation of AST on Day 63 (44). All other LFTs were within normal limits. No etiology was documented in the medical record.

Subject 9026 (a 20-year-old white male) had a minor elevation of AST on Day 7 (51). All other LFTs were within normal limits. The elevation was noted in the discharge summary but there was no assessment of etiology.

Subject 9027 (a 21-year-old Hispanic male) had a minor elevation of AST on Day 55 (47) and Day 56 (47). An elevated total bilirubin of 1.7 mg/dL was documented in the medical record, but there was no assessment of etiology. The subject admitted to occasional alcohol use on the medical history form.

Subject 9042 (a 25-year-old white male) had a minor elevation of AST on Day -1 (44), Day 4 (43), Day 14 (43), Day 28 (57), and Day 63 (44). AST returned to normal ranges on Days 1 and 2, as well as Days 7 through 11. There was no documentation in the medical record to explain the elevated LFTs nor was there a formal discharge summary sheet. Subject denied alcohol use on the medical history form.

Subject 9045 (a 26-year-old white male) had a minor elevation of AST on Day 28 (50). All other LFTs were within normal limits. Etiology was not addressed in the medical record.

Subject 9050 (a 21-year-old white male) had a minor elevation of AST on Day 14 (52) and Day 28 (43). By Day 62, AST was within normal limits. Etiology was not addressed in the medical narrative notes.

Subject 9055 (a 22-year-old white male) had a minor elevation of ALT on Day 4 (51) that was within normal limits at Day 7. The subject admitted to routine use of 12 beers per week on the medical history form.

Subject 9058 (a 20-year-old white male) had a minor AST elevation on Day 4 (46). All other documented LFTs were within normal limits. Etiology was not addressed in the medical record.

Subject 9028 (a 19-year-old white male) had an elevation of ALT on Day 28 (60) and Day 104 (74). All other documented LFTs were within normal limits. Etiology was not addressed in the medical record.

Subject 9033 (a 30-year-old Hispanic male) had an elevation of AST on Day 1 (49), Day 2 (48), Day 3 (52), Day 4 (74), Day 7 (66), and Day 210 (44). ALT was elevated on Day -2 (55), Day 1 (88), Day 2 (95), Day 3 (108), Day 4 (111), Day 7 (118), Day 11 (75), Day 14 (68), and Day 210 (71). All other LFTs were within normal limits. Subject admitted to occasional alcohol use on the medical history form, but etiology was assessed as "unknown."

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Subject 9035 (a 21-year-old white male) had an elevation of AST on Day 1 (43), Day 2 (70), and Day 4 (71); and ALT on Day 4 (54). Day 7 documentation indicates that the subject admitted to "considerable alcohol intake the night before."

Subject 9056 (a 24-year-old white male) had an elevation of AST on Day 2 (61), Day 4 (77), Day 7 (61), Day 9 (59), Day 11 (49), Day 14 (45), and Day 62 (46). ALT was elevated on Day 2 (77), Day 4 (156), Day 7 (126), Day 9 (138), Day 11 (110), and Day 14 (74). The discharge summary referred to these elevations as "mild." Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) labs were drawn but pending results at time of discharge. The subject admitted to routine use of 2 beers per week on the medical history form.

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